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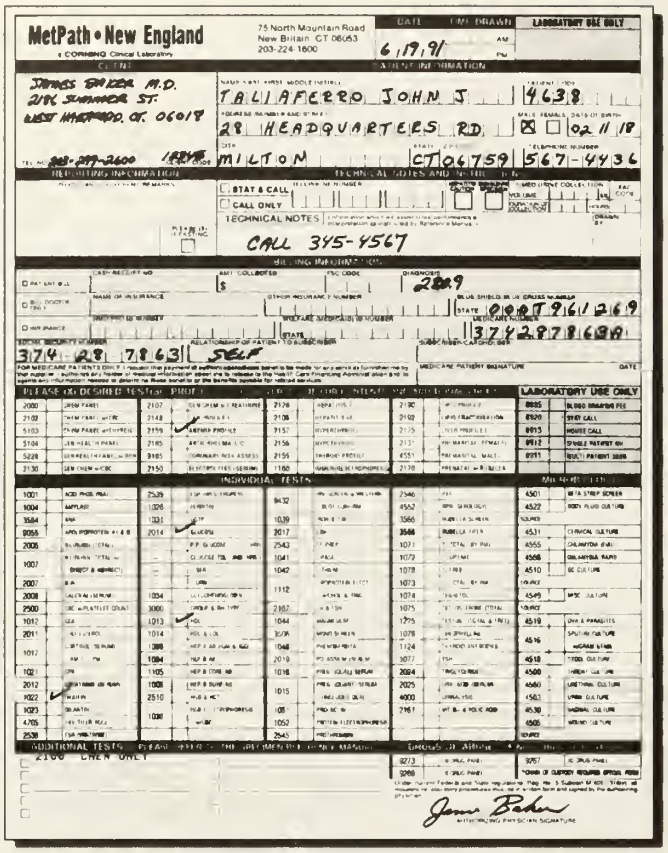
Recent Advances in Cardiology



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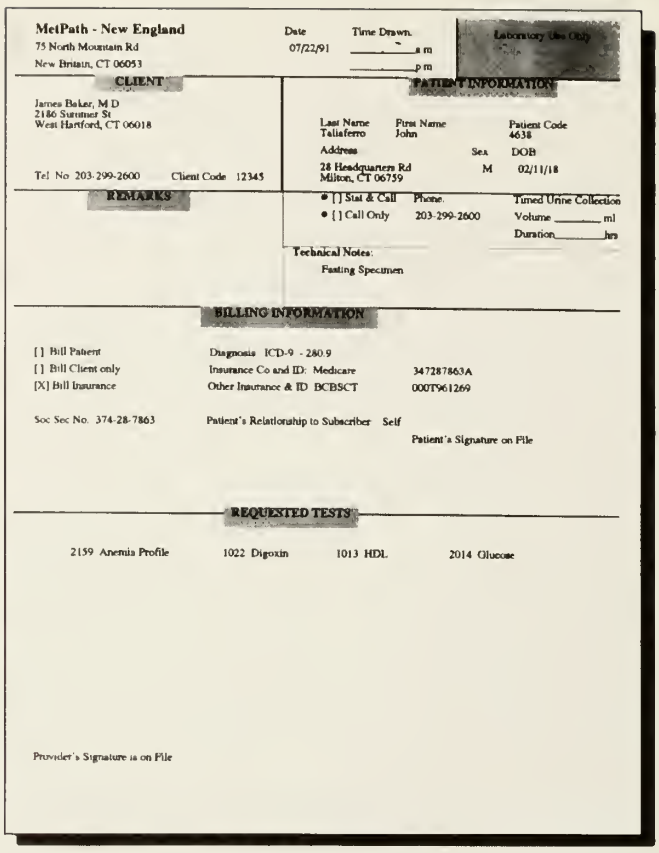

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Cover: Woodcut of Leonhard Fuchs (1501-1566), Professor of Medicine at Tubingen University. An authority on botany, Fuchs published an herbal in 1542 describing foxglove, giving it the name of digitalis, and advocating its use for dropsy.

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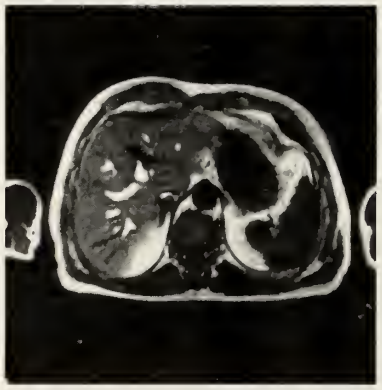

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COMMENTARIES

Imaging and Intervention in Cardiology

The past two decades have seen a quantum growth in cardiovascular diagnosis using less invasive modalities. Echocardiography and nuclear imaging techniques have been in the forefront of this explosive development. The earliest work in echocardiography began nearly four decades ago in Europe. However, it was the seminal work of Feigenbaum and colleagues in the late 1960s demonstrating pericardial effusions that spurred the use of echocardiography because it gave incremental information of value in clinical decision making. What has followed is well known to all of you. Echocardiography using two-dimensional techniques is now readily available not only in most community hospitals but in many practitioners' offices who specialize in cardiovascular diagnosis. Less well appreciated are further advances now ongoing in echocardiography which include burgeoning use of transesophageal echocardiography (TEE) as well as intravascular and intracardiac applications, and the introduction of contrast agents which promise to demonstrate myocardial perfusion and quantitative flow measurement.

Concurrent with the growth in ultrasound imaging has been the refinement of nuclear diagnostic techniques which have evolved from the early work of Pitt, Zaret, and coworkers at Johns Hopkins Medical Center. These early investigators showed that ventricular function could be quantified using gated radionuclide techniques and that myocardial perfusion abnormalities could be detected using potassium radioisotopes. Later refinements led to improved isotopes now widely employed to demonstrate myocardial perfusion in patients with coronary disease. A further evolution of nuclear imaging has been the use of positron emitters which can be incorporated into biologically active compounds. Positron imaging allows one to assess cellular metabolic activity and is now widely regarded as an important method to assess viability of dysfunctional heart muscle.

A number of other imaging techniques have also evolved for cardiovascular diagnosis concurrent with echo and nuclear techniques. These include computed tomography, cine computed tomography and magnetic resonance imaging, all of which hold future promise for even further refinement in cardiovascular diagnosis.

During the 1980s major breakthroughs also occurred in interventional therapeutic techniques in cardiology. A host of new pharmacologic agents have emerged including new beta-blockers, ACE-inhibitors, calcium channel blockers, and thrombolytic agents for patients with acute myocardial infarction. Now percutaneous transluminal balloon coronary angioplasty (PTCA) for patients with coronary disease has also made the cardiac catheterization laboratory a place for routine therapy and not just invasive diagnostic procedures.

This issue of the *Journal* attempts to bring a current level of understanding of some of the key techniques presently available for sophisticated cardiovascular diagnosis and therapy throughout the United States. Aebischer and colleagues point out the incremental value of transesophageal echocardiography in a number of clinical contexts. Tilkemeier and colleagues summarize the present status of nuclear cardiac imaging techniques emphasizing the information available with SPECT imaging, approaches to diagnosis using pharmacologic interventions and the status of newer imaging agents. Dr Henry Gewirtz details the promise of PET imaging showing its incremental value for assessing myocardial viability. Finally, Dr Kenneth Korr describes the use of PTCA as extended to the most critically ill patients with coro-

nary disease, those with acute myocardial infarction. There are further advances in our ability to revascularize the coronary circulation in the catheterization laboratory and we hope to be able to bring you added insight into some of these evolving techniques that have been used by Dr David Williams and colleagues in a subsequent issue of the *Journal*.

We trust that the information found herein will be helpful to you in your evaluation and treatment of patients. Certainly the authors of these articles who are all based here in Rhode Island would be most pleased to provide you with further information regarding these techniques and modalities insofar as may be helpful to you in your day to day practice of medicine.

Alfred F. Parisi, MD
Director, Division of Cardiology
Brown University Program in Medicine

Dr Withering's Remarkable Decoction

"In the year 1775 my opinion was asked concerning a family receipt for the cure of the Dropsy. I was told that it had long been kept a secret by an old woman in Shropshire who had sometimes made cures after the more regular practitioners had failed." Thus does William Withering, MD, FRS, practitioner of physick and Fellow of the Linnean Society, begin his enduring description of the therapeutic essence within the extracted leaves of foxglove (*Digitalis purpurea*).

Foxglove is a self-seeding biennial distributed widely throughout Europe, growing wild particularly in rocky and siliceous soils. It produces a solitary stem upwards of four feet in height, with alternate, rugose, dull-green leaves and – in late summer– generates multiple, lengthy, pendulous blossoms which assume the deep-throated shape of abbreviated finger cots. The name, foxglove, as it is currently known in the British Isles, is probably derived from the older term folks' (ie, fairy) glove. In Scotland it is still referred to as dead-man's gloves, in Wales, *menyg-ellyllon* (ie, elves' gloves), in France, *gants de Notre Dame*, and in Germany *Fingerhut* (ie, thimble).

William Withering, the English physician who recorded his extensive experience with digitalis leaf extract. Note the foxglove in his left hand.

In 1542, Leonhard Fuchs, the eminent Bavarian physician and botanist, published his text *De historia stirpium commentarii insignes* illustrating over five hundred botanical species which included the common (purple) foxglove. Because of the finger-like shape of its purple blossoms, Fuchs proposed that the plant be called *Digitalis purpurea*. Subsequent plant taxonomists accepted this name and assigned foxglove to the order *Scrophulariaceae* (a plant category containing the figworts which had once been thought to cure scrofula, hence the name of the Order). Other plants in this Order include snapdragon, veronica, speedwell and mullein.

Various herbal texts of the sixteenth and seventeenth centuries commended the leaves of foxglove for a variety of human disorders, but there is little attention directed to its unique effects upon edema until the 1785 Withering treatise. "I use it," Withering advised, "in the Ascites, Anasarca, and Hydrops Pectoris, and so far as the removal of the water will continue to cure the patient so far may be expected from this medicine: but I wish it not to be tried in ascites of female patients, believing that many of these cases are dropsies of the ovaria."

The Withering monograph identified foxglove as the pharmacologically active ingredient in the original mixture consisting of scores of herbs, then summarized the diuretic effects of various preparations (eg, decoctions, infusions, tinctures, powders), various concentrations and dosages, and the employment of various clinical endpoints (eg, "Continue the medication until the urine flows, or sickness or purging takes place").

His standard prescription was:

Rx. *Fol. Digital. purp. recent. oz.iv. coque ex Aq. fontan. purae lb iss ad lb i. et cola.*

Rx. *Decoct. Digital. oz. iss. Aq Nuc. Moschat. oz. ii. M. fiat, haust. 2dis horis sumend.*

Withering noted that the digitalis leaf seemed to work principally on edema of cardiac origin; and while he recorded that the strength of the pulse increased notably following its

use, he nevertheless believed that the leaf exerted its pharmacologic effects only upon the kidneys. Within the next decade, both Cullen and Ferriar published commentaries on the cardiotonic functions of digitalis extracts.

Digitalis purpurea

In his introduction, Withering stated that the therapeutic values of plants cannot be predicted solely by their chemical examination. Rather, he suggested, "Their virtues must therefore be learned either from observations of their effects upon insects and quadrapeds: from analogy, deduced from already known powers of some of their congenera or from empirical usages and experience of the populace." This statement could sit quite comfortably in any current text on experimental pharmacology.

Stanley M. Aronson, MD

The Language of Epidemiology (V): Stratified Rates

A rate is called crude when its denominator embraces an entire, typically heterogeneous, population. A crude rate is akin to counting all the vegetables in a store when our interest is directed solely to turnips. The crude birth rate (CBR) of a population, for example, is determined by the number of live births per year, divided by the mid-year population, multiplied by 100,000. Comparing the CBR of two regions clarifies little about their respective fecundity status unless we know the gender and age distribution of each population under scrutiny. If a particular population is composed predominantly of elderly males, the CBR will necessarily be low regardless of the fertility performance of its females. What is needed then is a measurement which is more focused upon the specific population under inquiry, such as the age-specific fertility rate which weighs only the fertility performance of females – and only those in a designated age range.

Similarly, the crude mortality rate of a population will rise if the average age of the population is increased, whether or not the basic health of the community has been altered. Rhode Island, with an older population than, for example, North Dakota, has a higher mortality rate. This does not necessarily signify that the health care provided locally is more deficient. Indeed, it tells us little until we can be provided with information regarding important variables such as the gender, age and ethnic composition of the respective populations of Rhode Island and North Dakota. In general, crude rates, whether of birth or mortality, are too insensitive and insufficiently discriminating to tell us much.

When, however, data are segregated according to important variables such as gender or age, the ensuing rates become more truly representative of reality. Such rates are then said to be stratified. For example, the fertility rate of women between the ages of 16 and 45 years (at a particular time and for a particular region) is far more revealing than is the crude birth rate of a total population which contains an unknown fraction of women within the age range of potential fertility.

The following example illustrates the critical importance of stratifying vital statistics. Note that the crude mortality rate (for major cardiovascular disease) was 485.7 (per 100,000 persons) in 1940, and then rose appreciably in each of the two succeeding decades. One would naturally conclude that heart disease, in the region described, was getting out of hand and that physicians in 1940 knew how to handle things better than their 1960 colleagues. The reverse, of course, was true, as a closer inspection of the data will demonstrate.

MORTALITY RATES FOR CARDIOVASCULAR DISEASE

Census Year	15-24 Yrs	45-54 Yrs	65-74 Yrs	All Ages*
1940	22.1	438.7	2,872.6	485.7
1950	13.5	411.5	2,609.0	510.8
1960	8.4	344.9	2,373.7	521.8

* Crude Mortality Rate for cardiovascular disease

When each age category is inspected it becomes apparent that mortality rates for cardiovascular disease have been significantly and uniformly lessened. In the 15 to 24 year old age category, for example, the deaths from bacterial endocarditis and rheumatic carditis had been dramatically reduced between 1940 and 1960. Similarly, the newer advances in the critical care of the patient with myocardial infarction, during this interval, served to delay death and therefore reduce the cardiovascular mortality rates in the elderly. Yet the crude mortality rate for this population rose in each of the succeeding decades by a cumulative 7.4%. The paradox is explained by the fact that this particular population, on average, had become older between 1940 and 1960. An increasing percentage had therefore entered the older decades of life at which time death rates rise dramatically.

By analogy, if one compared the lung cancer rates in college dormitories with those in homes for the aged, the latter would obviously be higher. But this would tell us nothing about the selective risk factors for lung cancer. To circumvent the problem of comparing dissimilar populations, we are obliged to diminish confounding factors, such as age, gender, and socioeconomic level, which may obscure the influence of the underlying risk factor(s) for the disease under study. We achieve this by insuring that the two (or more) compared populations are as similar as possible so that any emerging rate differences may then be confidently ascribed to some tangible divergency (eg, in diet, life style, occupation, exposure, etc) which distinguishes the two populations. Stratification of data serves to accomplish this.

Stanley M. Aronson, MD

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Transesophageal Echocardiography (TEE): Its Use in Today's Cardiology

Nicole Aebischer, MD
Alan Katz, MD
Candace McNulty, MD
Alfred Parisi, MD

Transesophageal echocardiography (TEE) has gained widespread popularity, with applications extending from the operating room to the ambulatory setting.

Since its inception transthoracic echocardiography (TTE) was somewhat limited by the structure interposed between the ultrasound transducer on the patient's chest and the heart. Patients with chest deformities (pectus excavatum, barrel chest), small intercostal spaces, obese patients, patients with chronic obstructive lung disease (COPD), patients with breast implants, and patients recovering from chest surgery are known to be poorly echogenic. In patients with COPD, lung expansion prevents the acquisition of adequate ultrasonic images since ultrasound waves propagate poorly through a gaseous medium. The loss of ultrasound as it travels through tissue is known as attenuation and varies in different tissues. It is lower for blood and greater for air and bone. As early as the mid-seventies, esophageal echocardiography has been used to record M-mode tracing in difficult patients to try to overcome the interference of lung or bony structures. Those early studies had all the limitations of the M-mode echocardiography. A few years later, real time two-dimensional images became available. However, the enthusiasm raised by the high resolution images obtained, was tempered by limitations in the available instruments.

Since then, the introduction of flexible endoscopes and transducer miniaturization have facilitated the clinical application of this imaging technique initially in Europe and Japan and more recently in the United States. In the past few years, color Doppler has been incorporated into the transesophageal transducer allowing better and faster assessment of intracardiac flow. To increase the scanning ability of the transesophageal probe, biplane transducers were introduced in the late 1980s. These new probes allow imaging of the heart in two orthogonal planes. Today, transesophageal echocardiography (TEE) has gained widespread popularity, with applications extending from the operating room to the ambulatory setting.

Nicole Aebischer, MD, is with the Division of Cardiology, Brown University Program in Medicine, Roger Williams Medical Center, Providence, Rhode Island.

Alan Katz, MD, is with the Division of Cardiology, The Miriam Hospital, Providence, Rhode Island.

Candace McNulty, MD, is Director, Doppler-Echocardiac Laboratory, The Memorial Hospital, Pawtucket, Rhode Island.

Alfred Parisi, MD, is Director, Division of Cardiology, Brown University Program in Medicine, Roger Williams Medical Center and The Miriam Hospital, Providence, Rhode Island.

ABBREVIATIONS USED:

COPD: chronic obstructive lung disease
TEE: transesophageal echocardiography
TTE: transthoracic echocardiography

Definition, Advantages and Safety of TEE

Transesophageal echocardiography is an imaging technique of the heart using an ultrasound transducer mounted at the end of a flexible endoscope. The procedure is a combination of two well known techniques: echocardiography and esophageal endoscopy. It is performed by a physician, usually a cardiologist, who has received additional training in endoscopy. In the operating room an anesthesiologist, well trained in echocardiography technique, may replace the cardiologist.

As outlined before, the enthusiasm about TEE lay in its capacity to obtain *High Resolution* images of the heart and great vessels. Because the esophagus lays just behind the heart, the image acquisition is unobstructed by interposition of poorly echogenic tissues, allowing the use of a higher frequency transducer with improved resolution.

... TEE can be performed at low risk if safety conditions are respected.

The drawback of the technique is that it is a semi-invasive procedure, not free of risk. In a recent publication, Daniel reviewed the experience of 15 European centers, performing TEE for at least one year. This is to date, the largest transesophageal echocardiographic study reported. A total of 10,419 TEE examinations were performed in the participating institutions, which represent 9% of the conventional transthoracic echocardiograms performed during the same interval. In awake patients, most of them without sedation, 88.7% of the TEEs were performed. Unsuccessful attempts to intubate the esophagus were reported in 0.88%. The reasons cited were patient's intolerance to the endoscope (65 patients), cardiopulmonary complications (16 patients), bleeding complications (2 patients), and other (7 patients). Among the cardiopulmonary complications there were 6 bronchospasms, 2 episodes of hypoxia, 3 non-sustained ventricular tachycardia, 3 transient atrial fibrillation, 1 third degree atrioventricular block, and one severe angina pectoris. One of the patients with bleeding complications died (mortality rate 0.0098%). The autopsy revealed a malignant lung tumor with esophageal infiltration. The author concludes that TEE can be performed at low risk if safety conditions are respected. A low rate of complications has also been reported by other groups in the United States. A recent echocardiographic-pathologic study also demonstrated that prolonged manipulation of the TEE transducer in the dog and monkey esophagus did not cause any mechanical or thermal damage. Currently, TEE appears to be a low risk procedure with a low complication rate and a very low mortality rate. However, as for any invasive procedure, the potential risk and benefit should be weighed for each patient.

Technique

TEE can be performed on awake patients in an ambulatory setting, on critically sick patients in the coronary or intensive care unit and in the operating room. Four to 6 hours of fasting is required as for any other upper endoscopy procedure. An intravenous line is started in the forearm and is used for medication. Topical anesthesia of the oropharynx is required to suppress the gag reflex. The use of low dose midazolam hydrochloride (Versed) IV in association with meperidine IV will cause light sedation and amnesia, particularly helpful in anxious patients. Intravenous diazepam is also frequently used. The use of a drying agent to reduce salivation is optional. There is still controversy about the use of antibiotics for endocarditis prophylaxis, but general consensus exists for routine prophylaxis in high risk patients such as those with prosthetic valves or pulmonary conduits.

In conscious patients, TEE is performed in the left lateral position. Vital signs and O_2 saturation are recorded throughout the procedure. Once the esophagus is intubated, imaging of the heart is usually started at 25-30 cm from the mouth. Different tomographic planes are obtained by manipulation of the probe.

Contraindications for TEE

Abnormalities of the esophagus like diverticula, stricture, varices, web or tumor are the major contraindications. In patients with a history of thoracic radiation, a barium swallow is recommended before the TEE as radiation is known to affect the esophagus. A gastroenterology consultation and upper endoscopy is recommended for patients suspected of esophageal disease.

Indications for TEE

Inadequate external acoustic window

Every patient in whom the conventional transthoracic approach is partially inconclusive or technically inadequate to assess left ventricular or valvular function is a potential candidate for TEE. This problem is com-

mon in patients with hyperinflated lungs, in patients with chest deformities, and in seriously ill patients confined to the intensive care unit, where a patient's mobility is limited and the lung's interference major because of artificial ventilation. This is also true for patients with chest trauma. For example, TEE should prove particularly useful in the detection of atrial tears resulting from blunt chest trauma. Atrial tears typically occur in the area of venous insertion or at the appendage where the wall is the thinnest. In those patients, the limitation of the chest window and the much higher resolution of the atrial structures obtained by TEE should favor the transesophageal approach. Figure 1 shows two basal short axis views of the right atrium and superior vena cava of a 26-year-old man with blunt chest trauma. The transthoracic imaging study was limited by severe pain and a sternal fracture and had been insufficient in quality to exclude cardiac injury. On the TEE examination, the thickness of both the right atrial free wall and interatrial septum appeared markedly increased due to edema and hematoma (Figure 1a). An adjacent thrombus is seen into the superior vena cava (Figure 1b). We believe that the TEE approach should also prove valuable in the evaluation of other cardiac injuries from blunt chest trauma. These include myocardial contusion, ventricular rupture, and ruptured chords of the atrioventricular valves. As there is also the possibility of esophageal damage from blunt chest trauma, we recommend that a barium swallow be performed prior to the TEE examination.

Besides technical limitations, there are conditions in which

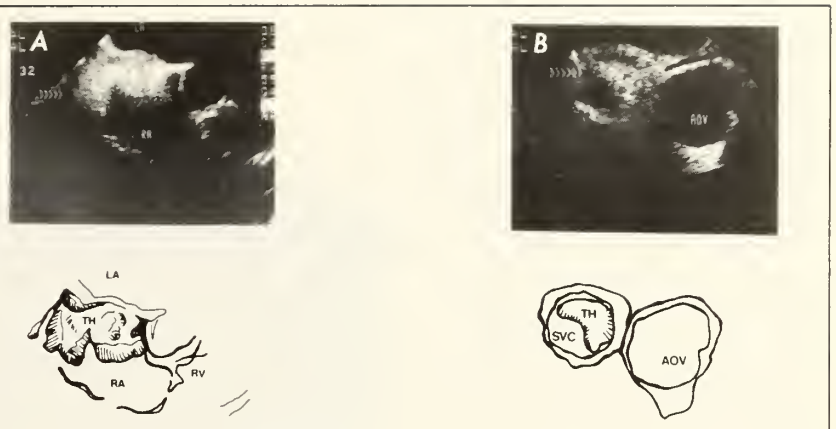

Figure 1.

a. Basal short axis view showing both atria and interatrial septum with schematic representation. A marked increase in the thickness of the right atrial free wall and interatrial septum (arrows) due to edema, hematoma and adjacent thrombus is noted. LA: left atrium; RA: right atrium

b. Basal short axis view of the superior vena cava and aorta with schematic representation showing the extension of the thrombus to the orifice of the superior vena cava (arrows). LA: left atrium; RA: right atrium

TEE has been shown to clearly improve the diagnostic information.

Prosthetic Valves

Although echocardiography using M-mode, two-dimensional and Doppler data have been useful in assessing prosthetic valves, TEE has become the method of choice to evaluate patients suspected of prosthetic valve dysfunction. Two different types of prosthetic valves are commonly used; the metallic and the biologic prosthesis. The metallic valves can be further sub-classified according to the occluder: the ball and disc-in-cage valves, the tilting disc and bileaflet prosthetic valves. Among the bioprostheses, the most commonly used are the porcine aortic valves and the bovine pericardium. Common to all the valvular prostheses is the masking phenomenon where the highly echo-reflective metallic portion of the prosthesis obscures the less echogenic tissue. For this reason visualization of small thrombi or vegetations attached to the valvular prosthesis, or degeneration of the valve leaflets is very difficult to detect using conventional TTE. One other problem specific to a prosthesis in the mitral position is the difficulty in grading mitral regurgitation because of the "flow masking" phenomenon. In the apical view from the transthoracic approach, the prosthesis is interposed between the ultrasound beam and the LA cavity, masking regurgitant flow. Because of its high resolution and the close proximity of the esophageal wall to the atria, the TEE provides more reliable information regarding potential structural abnormalities and permits a more accurate determination of mitral valvular regurgitation.

Intracardiac Mass

The transesophageal echocardiogram is very helpful in the assessment of patients with an intracardiac mass, particularly at the atrial level. Because of the close proximity of the atria to the transducer, TEE offers a magnificent view of both atria and related structures. The en-

try of the pulmonary veins into the left atrium and of the vena cavae and sinus venosus in the right atrium, as well as the entire interatrial septum are easily identifiable. If a mass is present, TEE will allow assessment of its size and mobility as well as its relation to other structures. From the transesophageal window both atrial appendages can be visualized, structures rarely seen from the transthoracic window. Visualization of the left atrial appendage is particularly important in the evaluation of patients presenting with possible embolic event of cardiac origin. Recent studies have shown that more thrombi are visualized in the left atrial appendage than in the left atrium itself (Figure 2). Spontaneous echo contrast, also reported as smoke-like echoes, have been reported increasingly in the left atrium of patients with mitral valve stenosis and after mitral valve replacement using transesophageal echocardiograms. This phenomenon has been observed in the past with the transthoracic approach in dilated and poorly contractile left ventricles but was rarely seen in the left atrium. In vivo and in vitro studies revealed that those echoes appear when blood flow is very slow. The presence of spontaneous echoes has been associated with a higher incidence of thrombus and embolic events.

It is our policy to recommend TEE in all patients presenting with embolic events thought to be cardiac in origin in whom an abnormal exam would alter clinical treatment. A transthoracic study should be performed first, since a positive study may make the TEE unnecessary but a negative study should not preclude the TEE examination. In addition, TEE will allow the visualization of small atrial septal defect, a patent foramen ovale (potential way for paradoxical embolism), an aneurysm of the interatrial septum, and of left atrial and left atrial appendage masses which are commonly missed by transthoracic imaging.

Figure 2. Magnified view of the LA and LAA with schematic representation. A long "snake-like" thrombus is seen in the LAA. LA: left atrium; LAA: left atrial appendage; T: thrombus

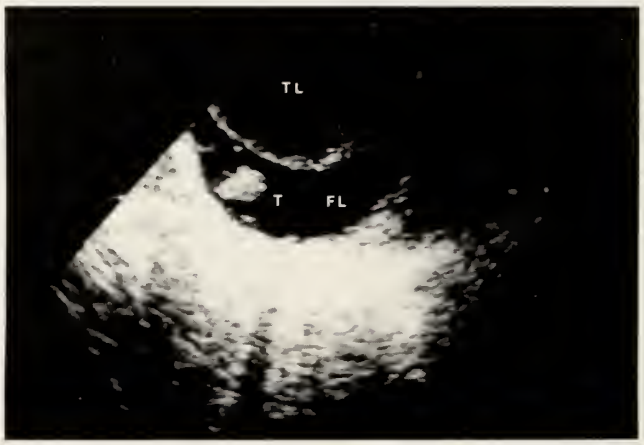

Figure 3. Cross-section view of the thoracic aorta. The true and false lumen as well as the intimal flap are nicely seen. A thrombus is also noted in the false lumen. TL: true lumen; FL: false lumen; T: thrombus

Endocarditis

In patients with the clinical diagnosis of endocarditis, who have a negative transthoracic echocardiogram, TEE has a potential benefit. Its high resolution will permit the visualization of vegetations too small to be seen by transthoracic approach or are in a position not accessible by conventional imaging. TEE will also better assess the severity of valvular regurgitation if present. As discussed earlier, TEE is clearly superior in detecting vegetations in patients with prosthetic valves. Another condition where

TEE appears far better than transthoracic echocardiogram, is the detection of abscesses associated with endocarditis. This condition is not uncommon, it has been diagnosed by autopsy or surgery in complicated endocarditis in about 30% of the cases. Because surgery is usually recommended for those patients with abscesses, an early and accurate diagnosis is essential. In a recent publication Daniel et al showed that TTE detected only 13 of the 46 surgically or autopsy-documented paravalvular or myocardial abscesses, whereas the TEE findings were accurate in 40 cases.

TEE has the advantage of real time imaging that can be performed at the bedside independently of the patient's condition.

Aortic Dissection

Aortic dissection is a condition which clearly needs prompt diagnosis and treatment to reduce the risk of death. Until recently, CT scan and angiogram of the aorta were used to assess patients suspected to have aortic dissection. Both techniques have their limitations with false positive and false negative studies and may be difficult to perform in patients presenting in shock. Both used dye and arterial access is needed to perform the aortogram. TEE has the advantage of real time imaging that can be performed at the bedside independently of the patient's condition. Valuable information regarding the location and the extent of the dissection, as well as the entry site and the presence of thrombus (Figure 3) can be obtained in a minimum of time. Echocardiographic imaging also has the advantage over the other techniques in diagnosing potential complications of aortic dissection involving the proximal portion of the aorta. These complications include pericardial effusion, aortic insufficiency, and coronary artery involvement by extension of the dissection into the coronary lumen or compression of the coronary artery by the dissection. For these reasons, TEE is becoming the method of choice for the diagnosis of aortic dissection. It has also been used to follow up patients who have had either surgical correction or medical treatment.

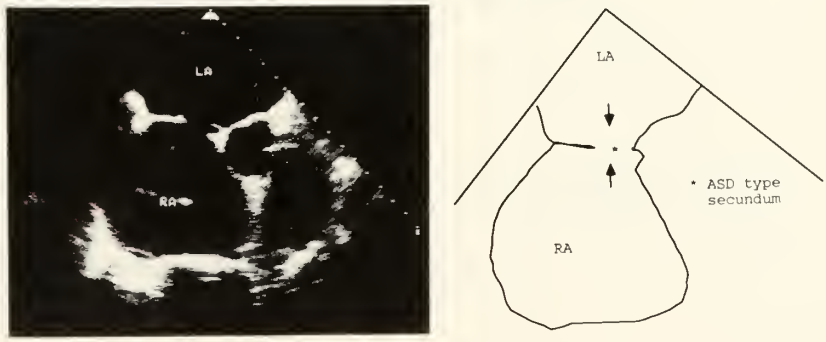

Figure 4. Magnified view of the LA, RA, and interatrial septum with schematic representation. A large secundum atrial septal defect (ASD) is seen. LA: left atrium; RA: right atrium

Congenital Heart Disease

Adults with congenital malformation, especially at the atrial level have benefited from transesophageal studies since its inception. With this method,

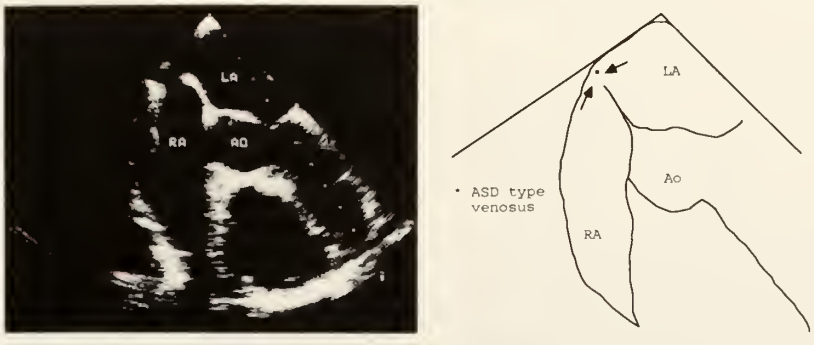

Figure 5. Magnified view of the upper portion of the interatrial septum and both atria with schematic representation. A sinus venosus ASD is seen on the upper portion of the septum. RA: right atrium; LA: left atrium; Ao: aorta

the type and size of atrial septal defects (Figures 4,5) can be clearly assessed as well as the possibility of associated abnormalities of venous return.

Since the development of a pediatric probe with a smaller diameter, TEE has been performed in children of all ages with success. TEE will clarify the atrial situs, as the different morphology of the right and left atrial appendages are easily identified. It can also detect abnormal venous return, defects in the inter-atrial and inter-ventricular septum, abnormalities of the valvular apparatus, malposition of the great vessels, and be very helpful in the setting of complex congenital disease.

Coronary Disease

Disease of the proximal portion of the left and right coronary artery system can be recognized by TEE. This can be particularly helpful, for example in the recognition of coronary aneurysm in children with Kawasaki disease.

Intraoperative TEE

TEE can be used in the operating room during cardiac and non-cardiac surgery to monitor left ventricular (LV) function in high risk patients. New or worsening of a pre-existing regional wall motion abnormality is an early index of ischemia, which may precede ECG changes by several minutes. Its early recognition by TEE will allow prompt treatment.

TEE is also of great value in the assessment of valvular surgery, for both repair of native valves and of replacement surgery. It permits detection of valvular or peri-valvular leaks and in the case of mitral valve surgery to assess for potential obstruction to the LV outflow before the patient's chest is closed. This has the advantage of allowing further surgical correction in the same setting.

Conclusion

TEE is a relatively new imaging technique of the heart which, because of its high resolution capability and different window, complements the conventional TTE. The introduction of biplane and soon multiplane transducers will allow acquisition of multiple unrestricted imaging planes of the heart and great vessels. Although it is a semi-invasive technique, its safety has been well established, when it is used in selected patients in the appropriate setting and performed by a physician well-trained in the endoscopic and echocardiographic techniques.

Suggested Reading

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Address correspondence to:
Nicole Aebischer, MD
Division of Cardiology
Roger Williams Medical Center
825 Chalkstone Avenue
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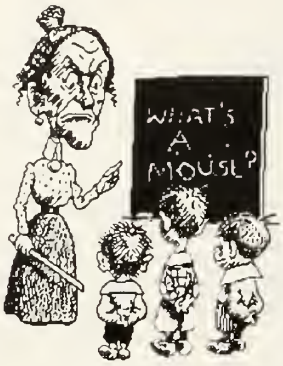
Computer Lessons



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Nuclear Cardiology: New Perspectives for the 1990s

Peter L. Tilkemeier, MD
Mark I. Travin, MD
Gary V. Heller, MD, PhD

... myocardial perfusion imaging... has become the most widely used noninvasive modality for assessing ischemic coronary artery disease.

Within the last fifteen years, myocardial perfusion imaging with thallium-201 has become the most widely used noninvasive modality for assessing ischemic coronary artery disease. Despite the success, new approaches to stress testing, recent advances in the computer sciences, and the introduction of new radioisotopes for imaging has greatly expanded the field of nuclear cardiology. These advances have allowed improved diagnostic accuracy for coronary artery disease and extended testing to patients who were previously unable to be evaluated noninvasively for coronary artery disease.

Alternatives to Exercise: Pharmacological Stress Testing

With the aging population and expanded indications for myocardial perfusion imaging, it has been found that a number of patients are unable to either exercise or complete an adequate exercise test. Reasons for such inability include physical limitations such as amputations, arthritis, or severe peripheral vascular disease. Others are unable to complete adequate exercise because of medications (beta blockers) or simply have poor exercise tolerance. Because of this, alternatives to exercise have been developed including atrial pacing, cold pressor testing, or pharmacologic means. The most successful and best studied is intravenous dipyridamole.

The mechanism of action of dipyridamole is most likely by induction of coronary hyperemia, the result of an elevation of endogenous plasma adenosine levels. Dipyridamole induced coronary hyperemia preferentially allows vasodilation of normal vessels over that of stenotic vessels which results in differential blood flow. This altered blood flow pattern results in preferential uptake of radiopharmaceuticals in normal tissue beds producing defects in the images in areas of stenosis.

When compared with exercise, dipyridamole has similar diagnostic power. In a study of pooled data of 215 patients, both dipyridamole and exercise imaging had sensitivities of 79% for the detection of angiographically documented coronary artery disease. In addition, there was no significant difference between the specificity of 95% for dipyridamole and 92% for exercise. The presence of anginal chest pain during the dipyridamole infusion did not predict significant coronary artery disease. ST/segment depression occurred in approximately 20% of the patients undergoing dipyridamole testing and was more likely to occur in

From the Division of Cardiology and Departments of Medicine, The Miriam and Roger Williams Hospitals, Providence, and The Memorial Hospital of Rhode Island, Pawtucket, and Brown University Program in Medicine, Providence, Rhode Island.

ABBREVIATIONS USED:

BATO: Boronic acid adducts of technetium oxime
COPD: chronic obstructive pulmonary disease
LAO: Left anterior oblique
SPECT: Single photon emission computed tomography

patients with coronary artery disease than in those without. In addition, increased thallium lung uptake following dipyridamole is less frequent than with exercise and correlated only with the presence of, not severity of, coronary artery disease.

The side effect profile of dipyridamole includes flushing or a mild headache in approximately 40% of patients, and chest pain ranging from 20% to 40% of patients. Other side effects include shortness of breath and nausea or vomiting in about 10% of the patients. The frequency of side effects in our laboratories (over 2000 patients) has been less than that in the early literature. Indeed, serious side effects from all studies are rare.

An absolute contraindication to dipyridamole imaging is a history of asthma or bronchospasm since adenosine can induce broncho-constriction in these patients. Asthmatic patients on long-term theophylline therapy who cannot safely discontinue this medication should not be given intravenous dipyridamole. Those patients who are treated with inhaler therapy alone will in most cases tolerate the infusion of dipyridamole and may be evaluated in some laboratories. Patients who are recovering from recent respiratory distress or have any respiratory distress at the time of the dipyridamole infusion are at high risk for severe broncho-constriction and the possible need for intubation and should not receive dipyridamole. However, patients with COPD who may not have a bronchospastic component to their disease and can be discontinued from bronchodilator therapy for one week may be safely tested. Patients must also be off all xanthine derivatives and caffeine products for at least 48 hours prior to administration of the dipyridamole to achieve an adequate effect. The decision to use dipyridamole intravenously in a patient with lung disease is one that is best made following consultation between the physician performing the test and the patient's private physician. Only with this clinical consultation can careful judgement be utilized to expose the patient to the least amount risk.

A major indication for dipyridamole myocardial perfusion imaging is the preoperative evaluation of patients prior to peripheral vascular surgery.

If patients develop difficulty during the test, the effects of dipyridamole can be promptly reversed with intravenous aminophylline. In some laboratories, including ours, aminophylline is administered to all patients following dipyridamole imaging.

Other Indications for Pharmacologic Stress Testing

A major indication for dipyridamole myocardial perfusion imaging is the preoperative evaluation of patients prior to peripheral vascular surgery. Although the presence of ischemia during dipyridamole myocardial perfusion imaging is not an absolute contraindication to vascular surgery, it predicts a significantly increased risk of a perioperative cardiac event. A recent study by Eagle et al showed that the presence of ischemia is particularly serious in patients with prior Q-wave myocardial infarction, a history of angina, history of heart failure, the presence of an S3, or a Goldman index of greater than 7. Strong consideration should be given to preoperative cardiac catheterization in patients with these findings.

Dipyridamole is also useful in patients with poor exercise tolerance or on beta blockers who are likely to have an inadequate heart rate response to exercise. The combination of dipyridamole with limited exercise allows both the assessment of maximal myocardial ischemia and limited exercise tolerance. Limited exercise decreases splanchnic blood flow, thus lessening splanchnic uptake of the radiopharmaceutical and improves image quality. Dipyridamole imaging has also been shown to be safe in the early evaluation of patients following myocardial infarction. Trials to evaluate its prognostic utility early after myocardial infarction are presently recruiting patients.

In summary, the use of intravenous dipyridamole myocardial perfusion imaging has become a common alternative to exercise testing, particularly in the pre-operative evaluation of cardiac risk. In addition, it offers an excellent alternative or adjunct to exercise in those patients not able to exercise sufficiently.

A second agent for pharmacologic stress is adenosine. Adenosine is currently available for use in small doses for conversion of supraventricular tachyarrhythmias. In larger doses adenosine has been used investigationally for non-exercise assessment of ischemic coronary artery disease. As discussed above, it is thought that the mechanism of dipyridamole induced vasodilation is through increasing circulating adenosine levels. Preliminary data suggests adenosine may be infused instead of dipyridamole. As a result of its very short half life (less than 10 seconds), ad-

enosine clears rapidly from the blood pool and must be administered via continuous intravenous infusion.

. . . the use of intravenous dipyridamole myocardial perfusion imaging has become a common alternative to exercise testing, particularly in the preoperative evaluation of cardiac risk.

Side effects are consistent with the hyperemic effects of adenosine. These include headache, flushing, nausea and a drop in blood pressure. Atrio-ventricular block has been reported which resolves spontaneously. If severe side effects do occur, the dosage can be decreased and the symptoms will usually resolve in a short time period due to the very short half life of the agent. Aminophylline can be used to reverse these side effects if necessary, but is rarely used. The contraindications are similar to dipyridamole. Patients with asthma, COPD, or other respiratory conditions cannot be given adenosine. There is no exercise component in the testing protocol due to adenosine's short half life. The use of this agent, thus, does not allow the assessment of any exercise tolerance data. While adenosine is still an investigational agent it is doing well in clinical trials and its release is expected soon.

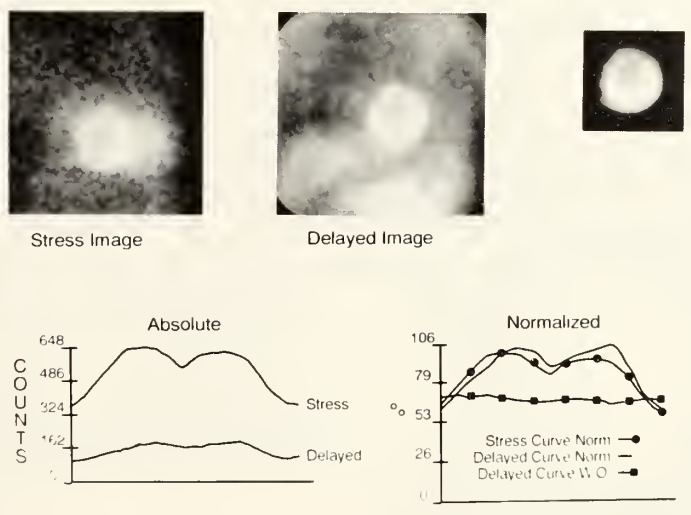

Figure 1. Planar Quantitative Format–Stress and redistribution images (LAO projection) are in the upper left corner. Bottom left graph displays the absolute myocardial counts at stress and redistribution. These curves are normalized for decay of the radioisotope in the normalized graph. This study is normal since the stress and redistribution normalized curves match and lie within normal limits for the lab. Areas of ischemia would be shown on the upper right hand image.

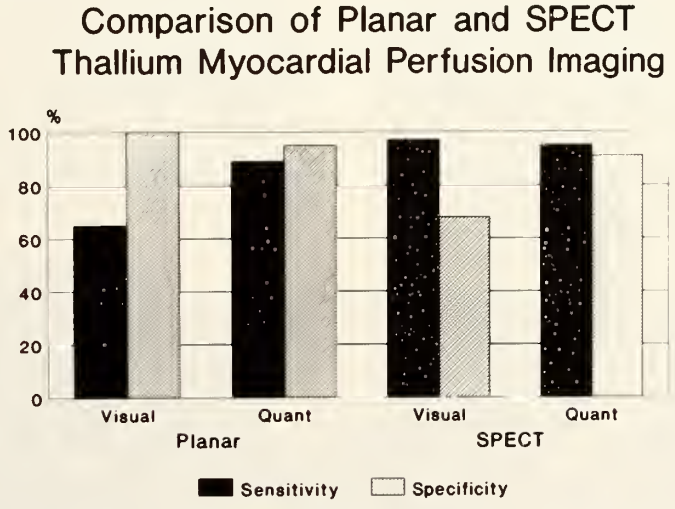

Figure 2. Comparison of the sensitivity and specificity of visual and quantitative analysis of both planar and SPECT images.

Computer Quantitation

Beginning in the mid 1980s, the development of faster computer processing allowed computer analysis of thallium images. Computer quantitation has become an important adjunct to visual image interpretation. There is significant inter- and intra-observer variability from visual analysis alone. Computer analysis allows objective interpretation of the thallium images, reducing this variability. Various commercial packages allow quantitation of the activity in the myocardium at stress and at rest, and are also able to correct for the time differential between the two images.

Quantitative analysis of planar images allows for enhanced assessment of 1) the presence or absence of a perfusion defect; 2) distinguishing between defects that redistribute (ischemia) or are fixed (infarction); 3) clearance or washout rate of radionuclide from the

myocardium, allowing further assessment of the presence of coronary artery disease; clearance values appear to be particularly useful in assessing the presence of multi-vessel disease; and 4) prognostic indicators such as increased lung uptake or left ventricular cavity dilation. This is of particular importance in the assessment of patients following myocardial infarction. A typical planar quantitative format is shown in Figure 1.

The application of quantitative techniques to planar images resulted in an increase in the diagnostic accuracy of thallium imaging for the detection of coronary artery disease.

The application of quantitative techniques to planar images resulted in an increase in the diagnostic accuracy of thallium imaging for the detection of coronary artery disease. The sensitivity increased approximately 24% from 65% with visual analysis alone to 89% with the addition of quantitative processing. The specificity decreases lightly from 100% with visual analysis to 95% with quantitation (Figure 2). While the computer provides a valuable objective second opinion in the image interpretation, it will misinterpret artifacts producing false positive tests–hence the need for all exams to be reviewed by an experienced reader.

SPECT Imaging

Standard three view planar imaging is limited by poor lesion contrast, spatial overlap of myocardial regions, and variable attenuation of non-cardiac structures such as the breast and chest wall musculature. A new imaging technology, Single Photon Emission Computed Tomography (SPECT) helps to overcome these limitations. This technology was developed in the late 1980s and involves further computer processing of the images. SPECT myocardial perfusion imaging is performed by rotating a camera through a 180-degree arc from 45 degrees right anterior oblique to 135 degrees left anterior oblique acquiring a series of 32 to 64 planar images from which background is excluded and filters are applied to allow reconstruction of the myocardium in various planes. Three sets of reconstructed images are displayed: 1) short axis views slicing from the apex to the base of the heart perpendicular to the long axis; 2) the vertical long axis slices, slicing

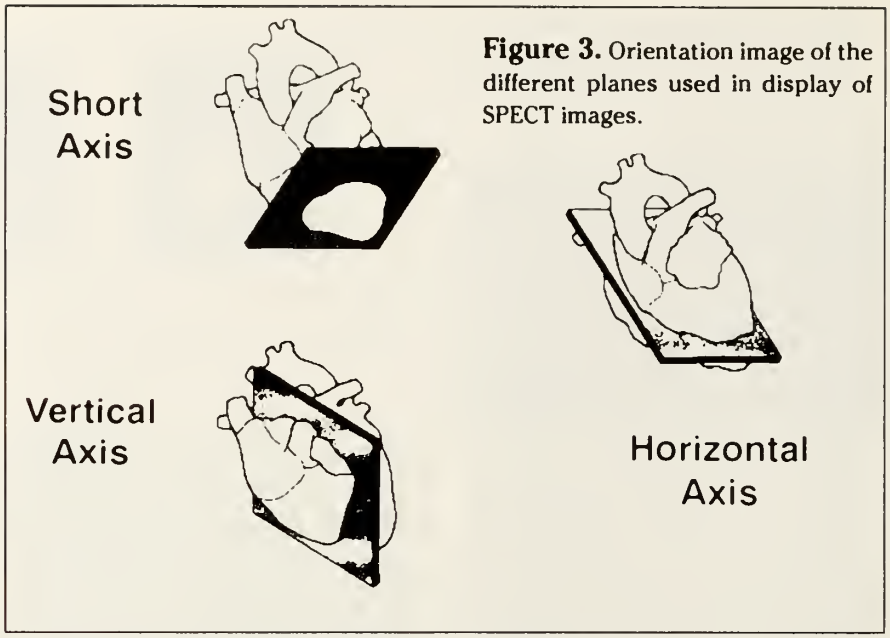

Figure 3. Orientation image of the different planes used in display of SPECT images.

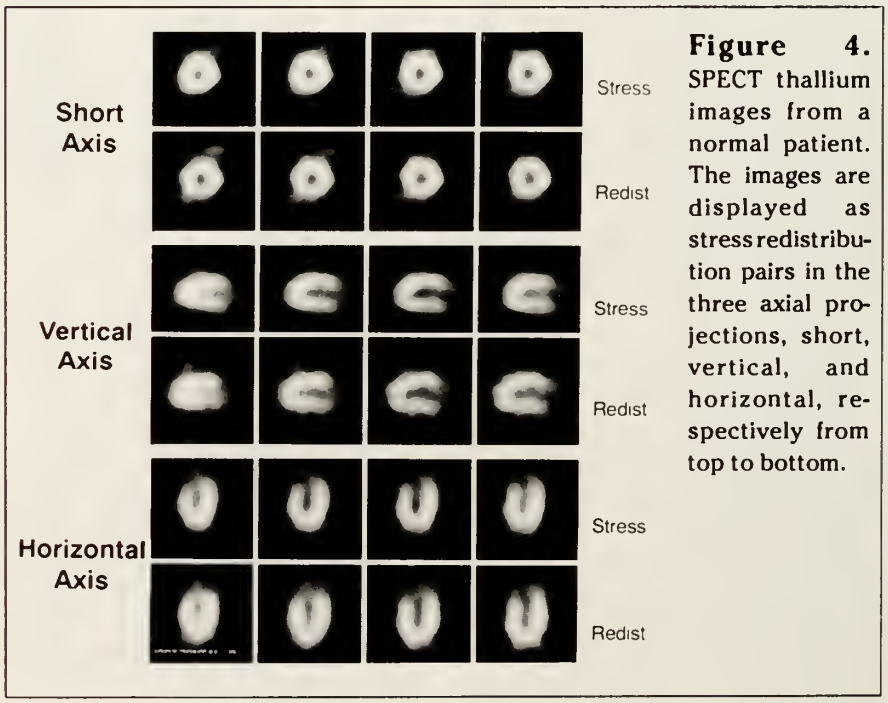

Figure 4. SPECT thallium images from a normal patient. The images are displayed as stress redistribution pairs in the three axial projections, short, vertical, and horizontal, respectively from top to bottom.

from the septum to the lateral walls of the heart; and 3) the horizontal long axis slices oriented parallel to the inferior and anterior walls of the heart (Figure 3). Due to the numerous processing steps involved in reconstructing SPECT images, careful consideration of quality control, count density, and patient motion or attenuation is important. Images are acquired both at stress and at rest and are processed identically. Approximately 10-12 slices in each of the three views are displayed and compared at stress and rest visually for perfusion abnormalities. This comparison can result in greater than 48 images to compare per patient, in contrast to the three images obtained with planar imaging. As a result of the greater number of slices generated and the circumvention of overlap, the SPECT technique is more accurate than the planar technique for identifying vascular territories that have abnormal perfusion. A sample display of four slices from a normal patient is shown in Figure 4.

To simplify this comparison, a further processing step can be utilized to generate a polar coordinate plot, also known as a "bull's eye" image. This image is a combination of the multiple images obtained through the reconstruction process. Specifically, the apex is displayed as the center of the circle. The short axis slices from the apex to the base are then displayed concentrically about the apical slices to allow a single view of the heart. This display format can be used to display both the stress and redistribution data along with other displays comparing data between two image sets.

The stress images can be compared to a "normal" population as they were in planar imaging. This allows determination of the extent of ischemia at stress. This stress extent bull's eye plot will show the areas of the myocardium that are normal (white), borderline (gray), or abnormal (black). This analysis gives the interpreter a non-biased opinion regarding the myocardial perfusion and the probability that a defect is real. Figures 5 and 6 show a normal display and a patient with circumflex coronary artery disease, respectively.

In addition to stress extent plots, other bull's eye maps can

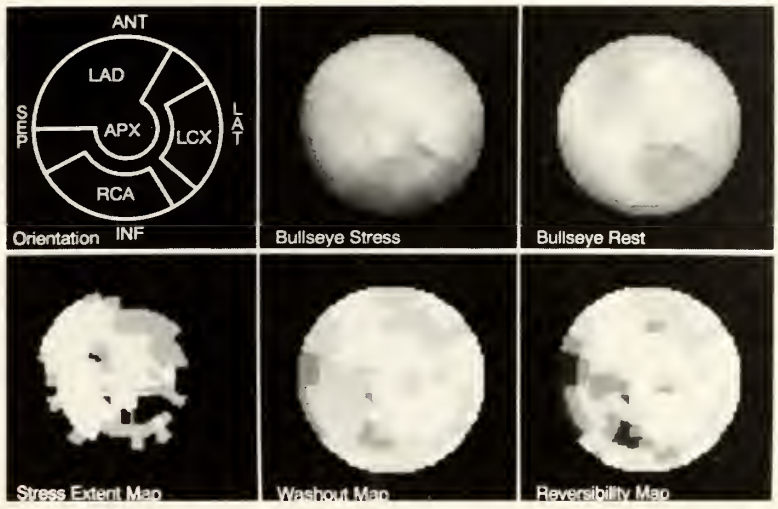

Figure 5. Typical polar coordinate (bull's eye) plots from a normal SPECT study. The top row has an orientation image, and the stress and redistribution plots. The bottom row of images shows the stress extent, washout and reversibility maps. In all plots white is normal, gray is borderline , and black is abnormal. ANT=anterior, LAT=lateral, INF=inferior, SEP=septal, LAD=left anterior descending, LCX=left circumflex, RCA=right coronary artery, APX=apex.

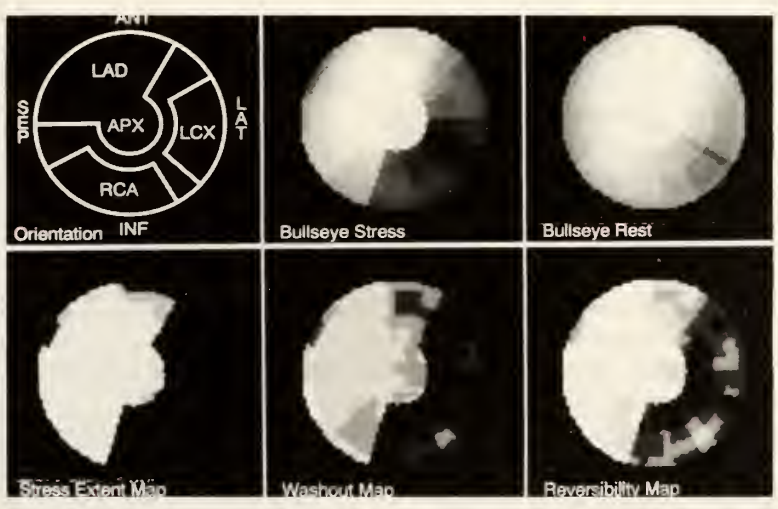

Figure 6. Polar coordinate (bull's eye) plots from a patient with circumflex ischemia. Format is identical to figure 5. A large reversible defect with low washout and significant reversibility is seen in the lateral wall consistent with circumflex ischemia. Abbreviations identical to Figure 5.

be used. The most common are the washout and reversibility maps. These are derived from a comparison of the delayed and exercise images. Knowing both the time interval between the images and the biological half life of the radioisotope used, both a washout time and the extent and severity of ischemia in a specific myocardial region can be calculated. Washout would be high for regions that are normally perfused (white or light gray) and low (black) for regions that are distal to a coronary artery stenosis. The reversibility map is divided into areas which are minimally ischemic or reversible (white) to areas which show more than 50% reversibility (black) as shown in Figures 5 and 6.

The use of these quantitative displays and SPECT imaging changes the sensitivity and specificity to 95% and 91% respectively. This is improved compared to visual analysis of the SPECT images alone and is even greater when compared with planar visual and quantitative analysis (Figure 2). SPECT imaging is of particular importance in the evaluation of right and/or circumflex coronary artery disease. The distribution of these two vessels is difficult to evaluate using planar imaging techniques, however, SPECT imaging has improved the sensitivity, specificity, and positive predictive value for the detection of disease in these two vascular territories (Figure 7).

. . . the SPECT technique is more accurate than the planar technique for identifying vascular territories that have abnormal perfusion.

Thus the development of faster computers has allowed the clinical application of new imaging techniques, providing increased diagnostic accuracy for detection of coronary artery disease compared with visual interpretation planar images alone.

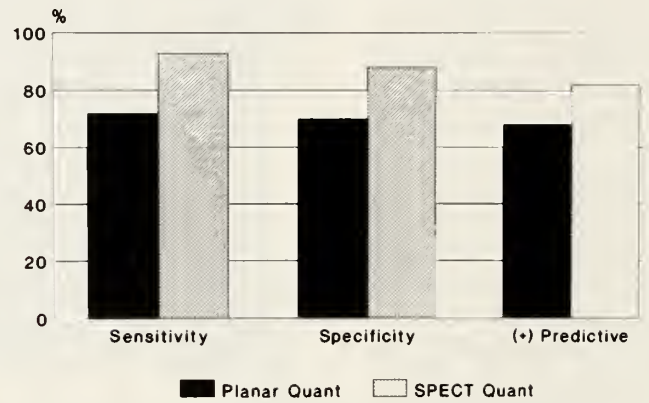

Figure 7. Comparison of the sensitivity, specificity and positive(+) predictive value of planar and SPECT quantitative imaging for either right coronary artery (RCA) or circumflex coronary artery disease.

New Technetium–99m myocardial perfusion imaging agents

Thallium is the most widely applied radiopharmaceutical used today for myocardial perfusion imaging. However, thallium has suboptimal physical properties for imaging. The more optimal radioisotope, technetium–99m, has a higher energy peak which decreases attenuation artifacts and a shorter half life allowing higher doses without increasing the radiation

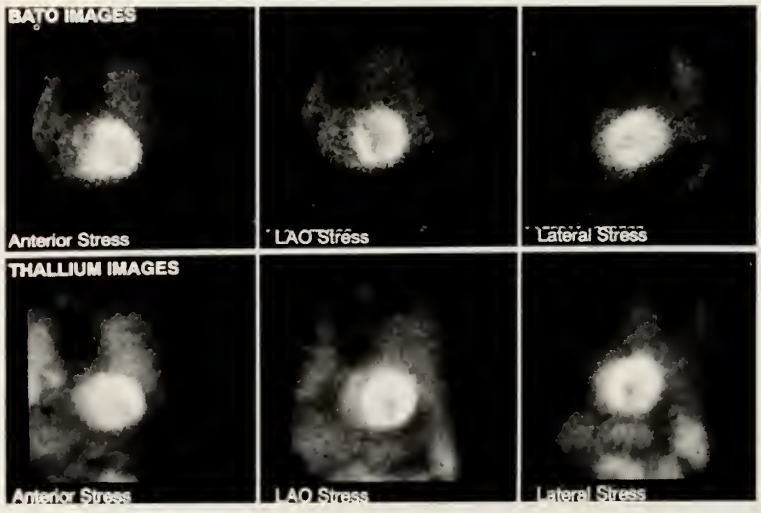

Figure 8. Typical planar BATO images compared to thallium images in the same patient. Note the decrease in image quality in the BATO images due to both the shorter imaging time and the faster washout from the myocardium. BATO images were acquired for one minute per view, thallium images for 8 minutes per view.

dosage to the patient. To date, two different myocardial imaging pharmaceutical preparations of technetium-99m have been developed. These are the boronic acid adducts of technetium oxime (BATO) compounds and the isonitriles.

The BATO compounds are extracted avidly by the myocardium. However, these compounds have a very short half life in the myocardium and are rapidly cleared from the heart. Images need to be obtained almost immediately post exercise. This can be problematic depending upon the laboratory set up that is being used to stress the patient. The short half life makes it particularly difficult to acquire SPECT studies using these radiopharmaceuticals. The BATO compounds have a sensitivity and specificity that is similar to thallium-201. Although there is significant hepatic uptake in the majority of the patients studied, this does not interfere with the identification of abnormal vessels. Typical BATO images are shown in Figure 8.

A second class of technetium-based myocardial perfusion imaging agents, the isonitriles, also looks promising. The isonitrile compound sestamibi has recently been released for clinical use. This class is different from the BATO compounds in that it has no clearance from the myocardium. This allows separation of the injection and stress from the time of imaging which can be carried out anytime within 6 hours following the time of injection. Ideally, imaging should be done somewhere between 30-60 minutes following injection, and thus a complete rest-stress study can be performed in approximately 4 hours. Since there is no redistribution of the isonitriles, they require two separate injections, one at rest and one following stress. Currently most sites using this agent use a two day protocol. A single day protocol can also be used. Representative isonitrile images from a two day SPECT protocol are shown in Figure 9. The isonitriles have been compared with thallium studies and have been found to be similar in their ability to detect coronary artery disease. There have been multiple studies using both planar and SPECT imaging to evaluate the sensitivity and specificity of the isonitriles for coronary artery disease. These studies have found that the isonitriles have an increased specificity for single vessel coronary disease, especially in those vessels with a mild stenosis in the 50% to 75% range. No significant differences have been found in the sensitivity of the two imaging agents. However, the rest-stress protocol identified more reversible hypoperfusion than does the stress-redistribution thalliums study.

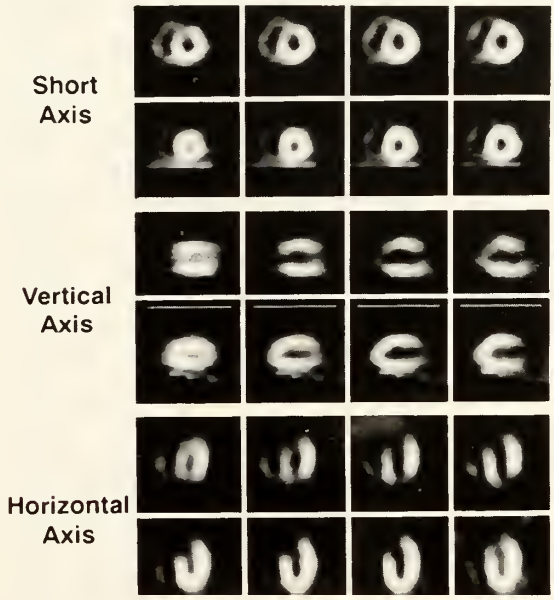

Figure 9. SPECT isonitrile images from an abnormal patient. The images are displayed as stress redistribution pairs in the three axial projections, short, vertical, and horizontal, respectively from top to bottom. There is a perfusion defect seen in the anteroseptal walls at stress that is normal at rest consistent with ischemia. Note the improved edge definition of the myocardium compared to thallium images (Figure 4).

The isonitrile compounds have also been used to identify the presence of myocardial infarction and they provide accurate information regarding infarct size. This has been documented in both phantom and animal models. An interesting use of the isonitrile compounds relates to its use in conjunction with thrombolytic therapy. If the patient can be injected with an isonitrile compound prior to receiving thrombolytic therapy, an image obtained within six hours will reflect the pre-thrombolysis myocardial blood flow distribution. This is possible because there is no redistribution of the compound following its extraction into the myocardium. A second injection can be given following treatment and a second set of images obtained, showing the area that had reperfused with the thrombolytic agent. This protocol has been used successfully at large university centers; however, because of the expense of the agent

and the time needed for preparation, this type of study is currently not routinely available.

Another use of the isonitrile compounds is the assessment of left and right ventricular function. This can be obtained by one of two methods. A first pass ejection fraction study can be obtained at the time of resting injection of the isonitrile compound. As the substance passes through the heart, data can be acquired showing the beat to beat ejection fraction. Data obtained with this method has been shown to have a high correlation with that from standard first pass methods.

The second method of evaluating ventricular function is with gated imaging following the standard imaging protocols for perfusion imaging. Due to the high energy characteristics of the technetium compounds, the images can be gated in either the planar or SPECT modes. This gating can then be displayed such that the actual myocardium can be seen beating similar to images obtained with an echocardiogram. As opposed to radionuclide ventriculography, gated perfusion images do not assess the effect of myocardial contraction of the blood pool, but instead directly allows visualization of myocardial contraction. Gated SPECT will display the image of the myocardium in a cine loop allowing visualization of both wall motion and perfusion in one set of images. The ability to evaluate wall motion simultaneous with perfusion is a unique one.

In summary, the field of nuclear cardiology is rapidly expanding given the capabilities of newer computers with rapid processing times that have allowed the introduction of new imaging techniques including SPECT myocardial perfusion imaging. This capability has allowed new quantitation modalities to be used to evaluate more objectively myocardial perfusion and allow comparison from patient to patient and from patient to normal populations. On the horizon is the further development of new technetium compounds that allow expansion of the studies that are able to be performed in patients. The advent of new pharmacologic stressing agents has also expanded the patient population that can be studied using nuclear imaging techniques and allows improved pre-operative assessment of cardiac risk. The wide spectrum of imaging modalities, processing techniques, and compounds that are now available to us, makes this a very interesting and diverse field that with recent developments permits improved diagnostic and prognostic information in all patients particularly those being evaluated either pre-operatively or post myocardial infarction. Hopefully, future developments in this field will lead to further improvements in the diagnosis and prognosis of coronary artery disease.

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Address correspondence to:
Peter Tilkemeier, MD
Division of Cardiology
The Miriam Hospital
164 Summit Avenue
Providence, RI 02906

PET Scanning in Evaluation of Ischemic Heart Disease

Henry Gewirtz, MD

. . . PET is capable of providing accurate, absolute measurements of myocardial blood flow and metabolism which previously could be obtained only by invasive methods.

Ischemic heart disease is the number one cause of death amongst adults in the United States. Although substantial gains have been made in recent years in the treatment of both acute and chronic forms of the disease (thrombolysis and coronary angioplasty are notable examples) comparable innovations in non-invasive evaluation of myocardial perfusion and viability have been much slower in coming and still are not widely available. The present review will focus on one emerging imaging technology, namely positron emission tomography (PET), and will endeavor to assess its utility in the evaluation of patients with known or suspected ischemic heart disease. An American Heart Association position paper regarding the use of PET for this purpose has recently been published.[1]

Henry Gewirtz, MD, is Director, Cardiac Research Laboratory, Rhode Island Hospital and with the Brown University Program in Medicine, Providence, Rhode Island.

What is PET?

PET employs special radioactive isotopes to form images of physiological processes with anatomical detail which are substantially better than conventional nuclear medicine techniques (5-7 mm vs 10-15 mm spatial resolution). The technology involved is both complex and expensive but can be summarized briefly as follows.

Certain isotopes of physiologically important atoms (eg, oxygen, carbon, nitrogen, fluorine and rubidium) decay by releasing positively charged electrons (positrons). Positrons after traveling a short distance through matter encounter negatively charged electrons and are annihilated. At the point of collision two high energy (511 KeV) photons are generated which fly away from one another in exactly opposite directions. The ability to detect these high energy photons and to measure accurately the extent to which they have been attenuated as they pass through the body on their way to the PET camera lies at the heart of PET technology.

Attenuation correction generally is not possible with conventional nuclear medicine techniques. The inability to correct for photon attenuation makes it impossible to determine absolute concentration for widely available tracers such as thallium or even the new technetium-99m labeled compounds, sestamibi and teboroxime in the heart and thus precludes measurement of absolute values of myocardial blood flow and metabolism with these isotopes. In contrast because PET technology permits absolute measurement of the concentration of a positron emitting radionuclide in the heart it is possible with

ABBREVIATIONS USED:

CABG: Coronary artery bypass grafting
FDG: Fluorodeoxyglucose
MRI: Magnetic resonance imaging
NIH/NHLBI: National Institutes of Health/National Heart Lung & Blood Institute
PET: Positron emission tomography
SPECT: Single positron emission computed tomography
Tl: thallium

mathematical models to make quantitative measurements of regional myocardial blood flow and metabolism. Further, because oxygen, carbon, and nitrogen all have positron emitting isotopes with half-lives ranging between 2 and 20 min, it is possible to label compounds of biological interest (eg, water, acetate and ammonia) and then trace either myocardial blood flow or metabolism under different physiological conditions (eg, rest and stress) in the same patient in just one imaging session. In summary, therefore, PET is capable of providing accurate, absolute measurement of myocardial blood flow and metabolism which previously could be obtained only by invasive methods.

In contrast to PET, X-rays and ultrasound have been developed and optimized to depict cardiac anatomy from which physiological inferences can then be drawn. Biochemical processes, however, are not directly imaged by these modalities. Ultrafast computed X-ray tomography also depicts anatomy for the most part and like PET and MRI (see below) still is very expensive and not widely available.

Magnetic resonance imaging (MRI) for the most part depicts anatomical information. It does so by means of powerful magnet fields, radio frequency pulses, and computers which are used to map the distribution of hydrogen atoms in the body and thereby create images of exquisite anatomical detail. Although magnetic resonance spectroscopy is capable of directly imaging physiological and biochemical processes the technology is still experimental, not widely available, and lacks satisfactory spatial resolution for cardiac diagnosis.

Table 1. **Average Sensitivity-Specificity of Thallium vs PET for Diagnosis of Coronary Artery Disease**

	Sensitivity	Specificity	N
Thallium	86% (85-96)	66% (52-80)	1298
PET	96% (93-100)	96% (78-100)	631

Note: Data abstracted from information in references 2-4 above. "N" refers to number of patients in reported series. Figures in parentheses indicate the range of values reported in the different series.

PET vs Standard Nuclear Cardiology Procedures

There is general agreement amongst experienced observers that PET images of the myocardium (Figure 1) are clearly superior to conventional thallium, sestamibi, or teboroxime images. The issue, therefore, is whether or not PET's technical superiority and potential for quantitative analysis of cardiac physiology is worth its price. Efforts to address this issue have usually begun with a comparison of the diagnostic accuracy of PET versus thallium.[1-6] Both the sensitivity and specificity of PET for the diagnosis of coronary artery disease have been very high in all reported series (>90% in almost all studies, Table 1). In contrast in some series sensitivity and specificity of thallium has been much lower (Table 1).

The issue of referral bias must be considered, however, when comparing studies in which both tests were not applied to all patients. Thus, apparent lack of specificity of thallium imaging for the diagnosis of coronary artery disease could reflect the fact that only patients with positive thallium tests are referred for cardiac catheterization, thereby excluding true negatives

Figure 1a: Tomographic sections of the heart are shown from a patient(KC) with previous anterior myocardial infarction. The scans depict myocardial blood flow as measured with $^{13}NH_3$. Note the clarity and anatomical detail of the images. An anteroapical defect is present and corresponds to the zone of infarction albeit with some residual flow (0.51 ml/min/g).
Myocardial blood flow in the lateral wall (1.71) was within the range of normal but was reduced in the interventricular septum (0.73). The later finding is consistent with hibernating, viable myocardium in the region and was confirmed by imaging with ^{18}FDG (fluorodeoxyglucose; Figure 1B). Abbreviations: 1=right ventricle; 2=interventricular septum; 3=anteroapical segment (left ventricle); 4=lateral wall (left ventricle); 5=liver

from published series. This happens because patients with a negative thallium stress test are usually not referred for catheterization and hence are not included in data analysis.

Two recent studies[3-4] compared thallium stress testing with PET (NH_3 or Rb) in the same group of patients all of whom underwent cardiac catheterization. In one study[3] thallium SPECT and PET (NH_3) were equally sensitive (95 and 98%). Specificity could not be meaningfully assessed since only 3 normals were involved and each was normal both by thallium and PET. Although the study of Tamaki et al[3] is often quoted as one which demonstrates that PET is no more sensitive than thallium SPECT, an important aspect of the study which has not received sufficient attention is the fact that nearly 80% (38/48) of the patients involved had suffered a myocardial infarction. There is little doubt that thallium imaging will detect most cases of myocardial infarction and thus the study population was heavily weighted in favor of "easy" cases so far as thallium imaging is concerned.

Another study[4] in which Tl SPECT and Rb PET were compared in the same group of patients indicated that PET was more sensitive and had greater predictive accuracy than Tl for the diagnosis of ischemic heart disease (95 vs 79% and 92 vs 78%, respectively). Specificity in this study was comparable (82 vs 76%). It is important to note the population of this study also was heavily weighted with infarct patients (107/202). Unfortunately no breakdown was available for results with infarct versus non-infarct patients. Nevertheless, the data from this and a number of other studies [1-4] indicate that PET likely is more specific and has greater predictive accuracy than Tl SPECT for the diagnosis of coronary artery disease (Table 1).

It is important to note the above analysis focuses only on the question of the diagnosis (yes-no) of coronary artery disease and does not address at least 2 other questions which are of equal or greater importance to the practicing cardiologist. Specifically, these questions relate to 1) assessment of relative and absolute coronary flow reserve and 2) the determination of myocardial viability. Both issues not uncommonly present in the same patient and both are of widespread interest especially in the current clinical environment with its focus on interventional therapies such as PTCA and thrombolysis.

Conventional nuclear cardiology procedures provide either purely qualitative or at best semi-quantitative information concerning relative coronary flow reserve (ie, comparison of one region in the heart to another under conditions of coronary vasodilation). This approach, while useful, is suboptimal for several reasons. First, qualitative analysis, which is most often employed in the clinical setting, depends on observer experience and training and is thus subject to bias. Similarly, inability to correct for photon attenuation artefact makes it difficult to assess relative flow reserve in women as well as very large or obese patients of either sex. In addition the relative nature of the assessment means it is necessary to assume that the myocardial region with best perfusion is normal, which may not be the case in patients with multivessel coronary disease.

Quantitative measurement of absolute values of myocardial blood flow would offer the prac-

... the data from this and a number of other studies indicate that PET likely is more specific and has greater predictive accuracy than Tl SPECT for the diagnosis of coronary artery disease.

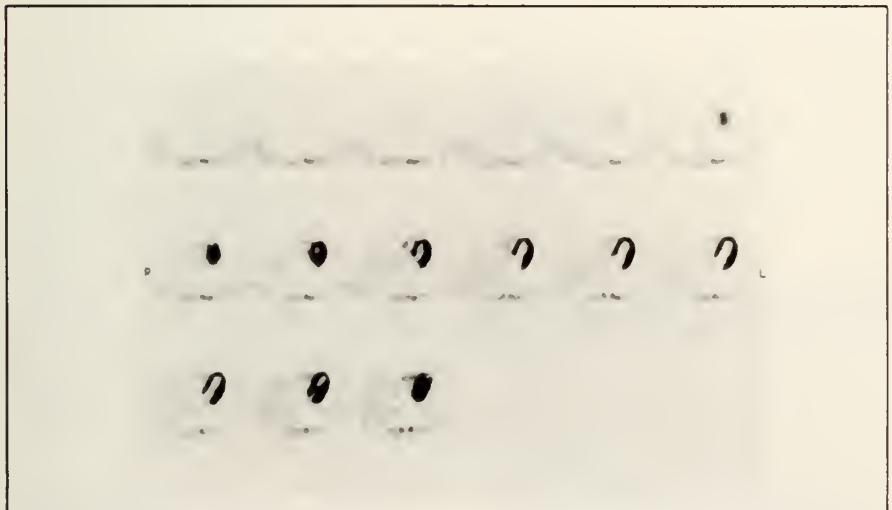

Figure 1b. Tomographic sections of the heart are shown here from the patient whose $^{13}NH_3$ blood flow scan is shown in Figure 1a. The images depict myocardial metabolism as seen with ^{18}FDG. There is evidence of preserved ^{18}FDG uptake in both the anteroapical and septal segments consistent with viable myocardium in both zones, notwithstanding the history of previous anteroseptal myocardial infarction (5,7).

ticing cardiologist a number of advantages over conventional assessment. The objective nature of this measurement should make them easier to use and more reliable in many respects. Correction for extraneous factors such as soft-tissue attenuation would facilitate evaluation for women as well as all who are very large or obese. Once normal values of myocardial blood flow have been established for carefully defined physiological conditions, it then would be possible to evaluate flow in all regions of the heart in a given individual and determine if it were normal, reduced or essentially absent. One could also assess absolute coronary flow reserve (increase in flow in a given vascular territory in response to a specific dilator stimulus under defined physiological conditions) and thereby obtain a more accurate assessment of the hemodynamic severity of a particular coronary stenosis independent to flow or status of other coronary vessels. Validation of mathematical models to measure absolute values of myocardial blood flow, flow reserve and metabolism have been reported from several laboratories.[1]

To use an analogy, reliance on essentially qualitative methods to evaluate coronary perfusion, flow reserve and metabolism is somewhat akin to employing simple palpation to determine a patient's temperature or blood pressure. If the patient is febrile enough or hypotensive enough one does not require a thermometer or sphygmomanometer to establish either fact. Simple palpation will do. However, if we wish to determine objectively and reliably which patients require treatment or to assess response to treatment or to determine better what type of therapy is most appropriate we need measuring devices such as the thermometer and sphygmomanometer. Unfortunately, noninvasive assessment of myocardial blood flow, flow reserve, and metabolism requires much more costly technology than the thermometer and sphygmomanometer. Nevertheless, the principle is still the same. Optimization of the diagnosis and treatment of patients with ischemic heart disease would be greatly facilitated by the availability of a modern objective method to make noninvasive, absolute measurements of myocardial blood flow and metabolism.

... were cost not a consideration, it is clear that PET should be used in all cardiac patients and could supplant all currently available conventional radionuclide techniques.

A related area of qualitative versus quantitative assessment of cardiac status concerns the issue of myocardial viability. At present subjective assessment of thallium myocardial images, either planar or SPECT, is at the heart of making this decision on a clinical basis. A recent report from the NIH/NHLBI[5] indicates that Tl SPECT with reinjection technique is equivalent to PET ^{18}FDG imaging for assessment of myocardial viability. The report is of considerable interest since it appears to demonstrate that the myocardial viability issue can be adequately addressed with a much less expensive and more widely available technology, namely Tl SPECT scintigraphy. It is important, therefore, to consider the NIH report in more detail.

First, it is worth noting that the patient population involved was both small (n=16) and highly selected. All patients had prior myocardial infarction, at least one apparently fixed thallium defect on standard stress redistribution imaging, and left ventricular dysfunction. In addition severe triple vessel disease was present in 10/16 patients but none had evidence of unstable angina or recent acute ischemia. The relevance of such a population to a more general mix of coronary patients including those with recent infarction or unstable angina without prior myocardial infarction is uncertain.

It also is of some interest to note that 2/3 cases of "irreversible" thallium defects shown in Figure 2 of the paper[5] appear to demonstrate clear cut evidence of redistribution in the standard redistribution scan. Thus even though the investigators were highly skilled and went to considerable efforts to be as objective as possible with the data, it is apparent that interpretation of clinical thallium scans may vary even when semi-quantitative methods are used. Further, as pointed out by Gould[6] in an accompanying editorial regarding the study, the ability of Tl SPECT to accurately size the amount of residual viable myocardium within or bordering the infarct zone was not addressed. Clinically available SPECT technology is not capable of attenuation correction and thus will not be able to size residual viable myocardium with the same accuracy and reliability as PET.

Summary

The question regarding the use of PET for the diagnosis and evaluation of treatment of patients with known or suspected ischemic heart disease is one of defining the proper test. The

data available indicate so long as relatively crude information is required that thallium (or new technetium labeled agents, sestamibi and teboroxime) may provide such information almost as well as PET. Examples include simple yes/no answers to questions such as 1) the presence of relatively advanced coronary disease or 2) amelioration of same with CABG or PTCA or 3) the presence of any viable myocardium bordering an infarct area. It also is clear that once more subtle or more precise information is required regarding response to therapy, functional significance of coronary stenosis, or extent of viable myocardium present that PET technology is superior to that of SPECT and therefore should be employed in the evaluation and treatment of patients with known or suspected ischemic heart disease. Finally, were cost not a consideration, it is clear that PET should be used in all cardiac patients and could supplant all currently available conventional radionuclide techniques.

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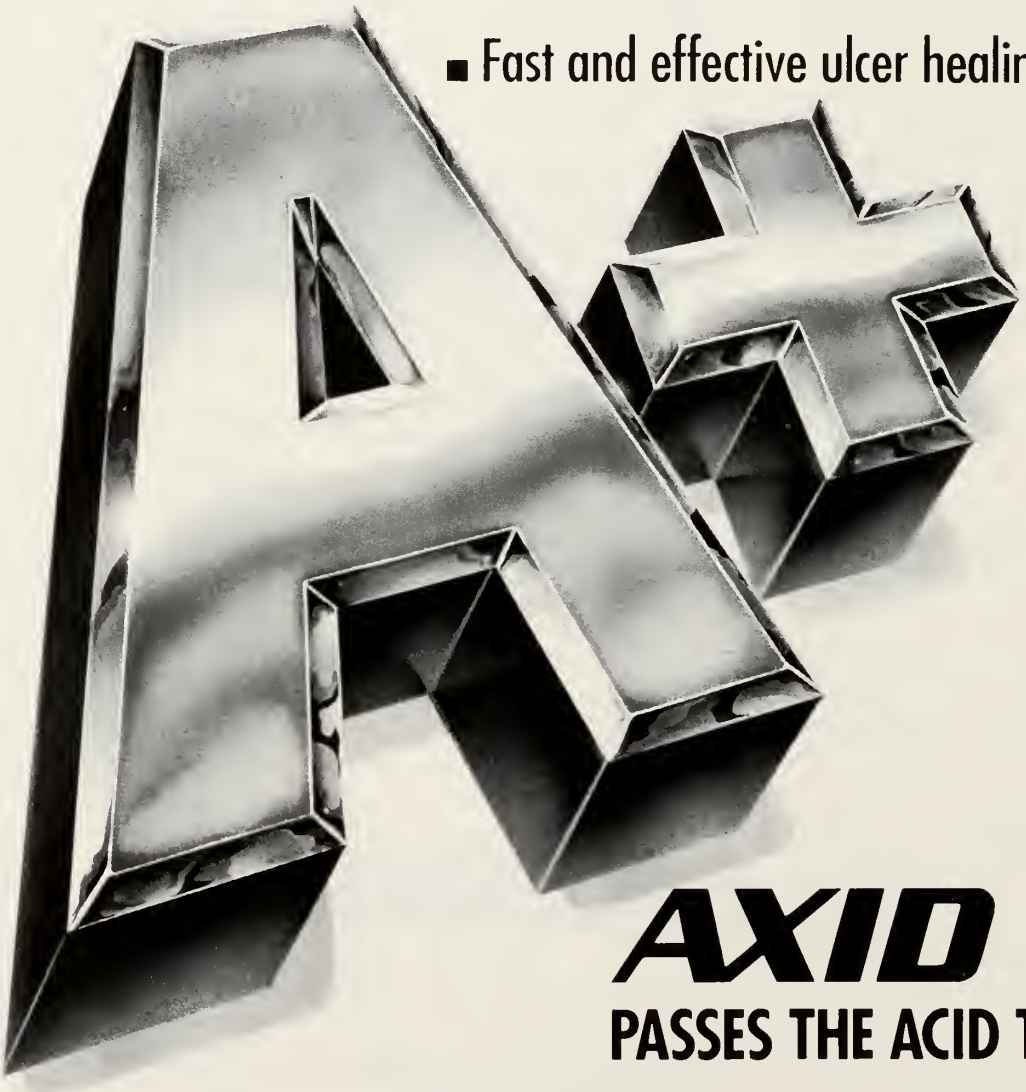

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Coronary Angioplasty in the Management of Acute Myocardial Infarction

Kenneth S. Korr, MD

The angiographic observations . . . provided irrefutable evidence that total thrombotic occlusion was the cause of myocardial infarction in the vast majority of patients.

The treatment of patients with acute myocardial infarction has undergone a dramatic evolution during the past decade. The angiographic observations of DeWood and his colleagues in 1980 provided irrefutable evidence that total thrombotic coronary occlusion was the cause of myocardial infarction in the vast majority of patients. Since then the emphasis of therapy has shifted from reducing myocardial oxygen demand to providing prompt restoration of coronary blood flow to the infarcted region in an effort to limit the amount of myocardial necrosis and ultimately to improve survival. Both thrombolytic therapy and coronary angioplasty (PTCA) have been successfully employed to achieve coronary reperfusion. Currently intravenous thrombolytic therapy is the simplest and most effective infarct intervention which can be applied to the vast majority of patients in the community hospital setting. However, thrombolytic agents are contra-indicated in a significant minority of patients because of potential life threatening bleeding complications. Furthermore, thrombolytic therapy may fail to acutely recanalize the infarct related artery in as many as 25% of patients. Finally, even in the setting of successful thrombolysis, a high grade residual stenosis frequently persists exposing patients to the risk of abrupt reocclusion and/or recurrent ischemic events. Thus, while thrombolytic therapy represents initial treatment for many and definitive treatment for some there is still an important role for coronary angioplasty in the management of patients with acute myocardial infarction.

Depending on the clinical setting, coronary angioplasty can be performed at a variety of times during the patients initial hospitalization for acute myocardial infarction. Several different PTCA strategies have been evaluated during the past decade (Fig. 1). In the early hours of acute infarction *Primary or Direct PTCA* can be performed in lieu of thrombolytic therapy. Alternatively, coronary angioplasty can be used in conjunction with thrombolytic therapy. *Immediate PTCA*, during or right

Kenneth S. Korr, MD, is Director, Cardiac Catheterization Laboratory, The Miriam Hospital, and Associate Professor of Medicine, Brown University, Providence, Rhode Island.

ABBREVIATIONS USED:

ECSDG: European Cooperative Study Group
EKG: Electrocardiogram
GISSI II: Gruppo Italiano per lo Studio della Streptochinasi Nell'Infarcto Miocardico
ISIS II: Second International Study of Infarct Survival
MI: Myocardial Infarct
NHLBI: National Heart Lung & Blood Institute
PTCA: Percutaneous Transluminal balloon Coronary Angioplasty
rt-PA: recombinant tissue-Plasminogen Activator
TAMI: Thrombolysis and Angioplasty in Myocardial Infarction trials
TIMI: Thrombolysis in Myocardial Infarction trials

after thrombolytic therapy infusion, is part of an aggressive strategy in which diagnostic coronary angiography is performed to define the overall extent of coronary artery disease and in particular the status of the infarct related artery. *Immediate PTCA* is done if there is a suitable coronary narrowing or occlusion supplying the area of infarction. This approach can be applied to a subset of patients who remain clinically and hemodynamically unstable following thrombolytic therapy and in whom there is a strong suspicion that thrombolytic therapy has either failed to recanalize the infarct vessel or that abrupt reocclusion has occurred. In this situation it is referred to as *"rescue" PTCA. Delayed PTCA* is an intermediate approach in which coronary angioplasty is performed 18 to 48 hours after thrombolytic therapy on all patients with a suitable narrowing or occlusion of the infarct related artery. It is based on the premise that following successful thrombolytic therapy a high grade residual stenosis frequently persists placing the patient at risk of recurrent ischemia or infarction. *Elective PTCA*, the most conservative strategy, is reserved for those patients who develop recurrent angina or objective evidence of inducible myocardial ischemia during hospitalization or following discharge.

Primary or Direct PTCA

In 1983 Hartzler and his associates were the first to describe their successful experience with primary PTCA as an alternative to intracoronary streptokinase plus PTCA in the treatment of patients with acute myocardial infarction. Since then other investigators have reported their nonrandomized retrospective

Figure 1. **PTCA Strategies in Acute Myocardial Infarction**

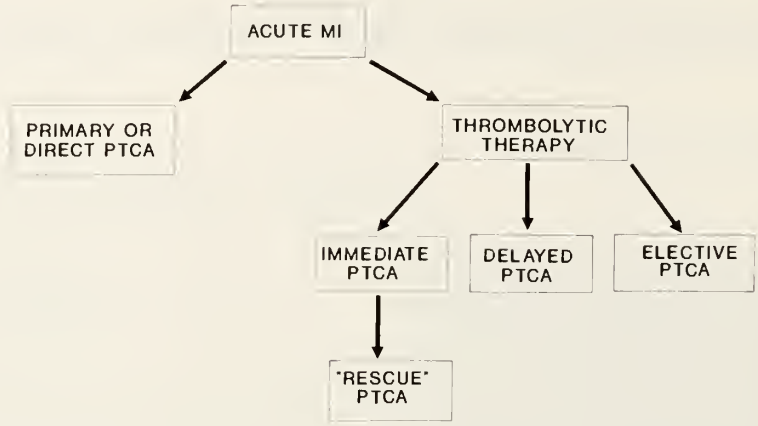


Figure 2. **Results of Primary PTCA in Acute MI**

STUDY	NO OF PATIENTS	SUCCESS RATE	IN-HOSPITAL MORTALITY	REOCCLUSION RATE
O'KEEFE (89)	500	94%	7.2%	15%
ROTHBAUM (87)	151	87%	9.0%	9.0%
MILLER (87)	127	92%	8.6%	7.9%
TOPOL (87)	47	86%	6.3%	-
O'NEILL (86)	29	83%	6.8%	-
KIMURA (84)	58	88%	-	-

Figure 3. **NHLBI PTCA Registry (1985)**

	AMI N=294 (%)	NON AMI N=1802 (%)	P
ANGIO SUCCESS*	88.1	82.2	<0.05
MORTALITY	5.1	0.9	<0.001
REOCCLUSION			
IN LAB	9.5	4.9	<0.01
OUT OF LAB	7.1	2.2	<0.001
DISSECTION	1.4	4.8	<0.01
EMERGENCY CABG	3.7	3.5	NS

*ANGIO SUCCESS = LESS THAN 50% RESIDUAL CORONARY STENOSIS

observations of direct coronary angioplasty (Fig. 2). Successful reperfusion of the infarct-related artery can be achieved in 83 to 94% of patients. In-hospital mortality rates range from 6.3 to 9% and abrupt vessel reocclusion occurs in 7.9 to 15% of patients.

Similar results were recently reported in the 1985 (NHLBI) PTCA registry (Fig. 3) which analyzed the results of primary PTCA in 294 patients with acute myocardial infarction compared to a larger cohort of patients undergoing conventional PTCA in the noninfarct setting. The angiographic success rate was similar in both patient groups (88 vs 82%). In-hospital mortality was significantly higher among the acute infarct patients (5.1 vs 0.9%) but was comparable to that reported from several large multi-center trials of intravenous thrombolytic therapy. Abrupt vessel closure occurred 2 to 3 times more frequently among patients undergoing primary PTCA (16.6 vs 7.1%). This high reclosure rate was probably the result of recurrent thrombus formation at the site of initial plaque rupture particularly since the incidence of coronary dissection (the only other potential cause of abrupt vessel closure) was so low (1.4%) among these patients. Adjunctive low dose intracoronary thrombolytic therapy to dissolve residual thrombus as well as adequate anticoagulation following primary PTCA has been advocated to reduce the frequency of reclosure.

Thus, the available data on the role of primary PTCA in acute myocardial infarction comes predominantly from nonrandomized observational studies in selected patients which may bias the results in favor of angioplasty. Nevertheless, these studies strongly suggest that angioplasty is clinically feasible with success rates comparable to currently available intravenous thrombolytic therapy. Whether direct PTCA offers any significant advantage over primary thrombolytic therapy in terms of survival or improvement in left ventricular function, however has yet to be tested among a large patient population.

. . . these studies strongly suggest that angioplasty is clinically feasible with success rates comparable to currently available intravenous thrombolytic therapy.

Patients with an absolute or relative contraindication to thrombolytic therapy are often ideal candidates for direct coronary angioplasty unless heparin therapy is also contraindicated. This setting was considered an acceptable indication for primary angioplasty in the "Guidelines for the Early Management of Acute Myocardial Infarction" recently published by the American College of Cardiology and the American Heart Association. In cases in which the patient is already hospitalized due to recent major surgery or trauma with an early diagnosis of myocardial infarction, direct coronary angioplasty may be the best option. In addition, patients in whom the diagnosis of acute myocardial infarction is equivocal (patients with left bundle branch block or other non-definitive EKG changes) may also benefit from a strategy of rapid diagnostic catheterization followed by direct PTCA, if appropriate.

PTCA in Cardiogenic Shock

Primary PTCA may play a particularly important role in reducing the high mortality of patients who develop cardiogenic shock secondary to acute myocardial infarction. Conventional medical therapy including intra-aortic balloon counterpulsation has proven ineffective in these patients with mortality rates in excess of 80%. Furthermore, the efficacy of thrombolytic therapy in this setting has been disappointing. The GISSI-I Trial documented no benefit from intravenous thrombolysis for patients who presented in Killip Class IV, and the GISSI-II Trial confirmed that the mortality rate among

Figure 4. **Multicenter Registry of PTCA in Cardiogenic Shock**

	SUCCESSFUL PTCA (N = 49)	UNSUCCESSFUL PTCA (N = 20)	
AGE	57	60.5	NS
MALES	67%	65%	NS
ANTERIOR MI	65%	65%	NS
MULTIVESSEL CAD	53%	80%	NS
IABP	74%	58%	NS
EJECTION FRACTION	32%	29%	NS
SHOCK TO REPERFUSION (h)	5	4	NS
7 DAY SURVIVAL	69%	20%	<0.0005
24 MONTH SURVIVAL	54%	11%	<0.003

cardiogenic shock patients treated with tissue plasminogen activator or streptokinase was still greater than 70%.

Several of the early reports of primary PTCA for acute myocardial infarction included small numbers of patients in cardiogenic shock. Survival rates among these individuals varied between 43 and 55%. Dramatically higher survival was observed for those patients in whom PTCA was successful compared to those in whom angioplasty failed (77% vs 18%). Similar results were reported when angioplasty was used in conjunction with thrombolytic therapy. Successful PTCA in these patients carried a mortality of only 15% compared with a 77% mortality for the unsuccessfully treated patients.

In the largest study to date, Lee and colleagues reported their experience with PTCA in 69 patients with acute myocardial infarction complicated by cardiogenic shock (Fig. 4). The majority of patients underwent treatment within 4 hours of symptom onset. Antecedent thrombolytic therapy with streptokinase in 29 patients was associated with a reperfusion rate of only 34%. In-hospital survival was significantly better in 49 patients who underwent successful PTCA compared with 20 patients in whom PTCA failed. (69% vs 20%). Successfully treated patients also enjoyed a better long term survival rate over 24 to 54 months follow up (54% vs 11%).

While all of these studies suffer from similar limitations including small numbers of patients, lack of an adequate control population and a mixture of therapies (both primary PTCA and rescue PTCA following failed thrombolytic therapy) the survival advantage of emergent PTCA is striking. Given the dismal prognosis for these patients treated conventionally, many groups now advocate immediate catheterization with intra-aortic balloon pump support, followed by emergent PTCA or coronary bypass surgery as anatomically indicated.

Figure 5. **Optimal Timing of PTCA in AMI**

	EARLY PTCA (N = 117)	LATE PTCA (N = 139)	P VALUE
TIME TO PTCA (h) (median, range)	4.5 (1.5 to 5.9)	15 (6 to 48)	<0.001
CARDIOGENIC SHOCK	11.2%	14.4%	NS
SUCCESSFUL PTCA	71.8%	78.4%	NS
RECURRENT ISCHEMIA	22.8%	15.6%	NS
EMERGENCY CABG	7.7%	3.6%	NS
IN-HOSPITAL (MORTALITY)	13.7%	13.7%	NS

Timing of Primary PTCA

Until recently most experts believed that reperfusion of the infarct-related artery was only beneficial if it occurred within 6 hours of the onset of occlusion. This belief was based on animal models in which significant myocardial salvage only occurred when reperfusion of the occluded artery took place within 3 to 4 hours. Most of the initial human studies of intravenous thrombolytic therapy seemed to confirm this concept. In the well publicized ISIS-II trial however, a significant survival advantage was observed in patients treated late, between 12 and 24 hours from symptom onset. This observation in such a large patient group raises significant practical questions regarding the optimal timing of reperfusion therapy.

Ellis and his colleagues retrospectively examined the results of early versus late primary coronary angioplasty without prior thrombolytic therapy performed in the setting of acute myocardial infarction (Fig. 5). All patients underwent coronary angioplasty on the basis of clinical evidence of ongoing ischemia (persistent precordial, arm or neck discomfort or electrocardiographic, ST and/or T wave changes) or hemodynamic compromise. The study patients were divided into an early group of 117 individuals treated with angioplasty within 6 hours of chest pain onset and a late group of 139 patients who received angioplasty 6 to 48 hours after the onset of chest pain.

The median time to angioplasty was 4.5 hours in the early group and 15 hours in the late group. The late group had more patients with diabetes mellitus (19.4% vs 7.4%; p=0.003), multivessel disease (61.2% vs 48.7%; p=0.05) and a lower ejection fraction (44% vs 49%; p=0.001). Successful angioplasty was accomplished in 71.8% of the early group and 78.4% of the late group. The overall in-hospital mortality rate was 13.7% in

both groups. Successful angioplasty, however, was associated with only a 5.5% in-hospital mortality compared with a 43.3% mortality after unsuccessful angioplasty ($p<0.001$). The predictors of hospital death were cardiogenic shock, lower ejection fraction, unsuccessful angioplasty and older age. The time to angioplasty was not a predictor of outcome.

The authors conclude that late emergency angioplasty may be justified when the likelihood of angioplasty success is very high. The study was limited by problems of patient selection, significant clinical differences between the early and late groups and the lack of a medically treated control population. In spite of this, however, the results suggest another therapeutic alternative for the significant minority (35%) of patients with acute myocardial infarction who present beyond the traditional 6 hour "therapeutic window". Furthermore they reemphasize the need for a randomized trial investigating possible survival benefits of delayed reperfusion in certain patients with acute myocardial infarction.

PTCA Following Thrombolytic Therapy

Coronary angioplasty as an adjuvant to thrombolytic therapy is intuitively attractive because it provides definitive treatment for the residual coronary stenosis that frequently persists following successful thrombolysis. The potential benefits of such therapy should include improvement in left ventricular function and enhanced survival as well as a reduction in the incidence of abrupt reocclusion and recurrent ischemic events. Experimental studies, however, have suggested that angioplasty may aggravate thrombus formation by increasing injury at the site of plaque rupture. Furthermore, invasive intervention early after thrombolytic therapy carries the risk of significant hemorrhagic complications. Thus the optimal timing of angioplasty following thrombolytic therapy has very real clinical implications. Three basic strategies have been tested in the last five years: immediate including "rescue" PTCA, delayed or deferred PTCA and the conservative strategy of elective PTCA performed only for recurrent or inducible ischemia.

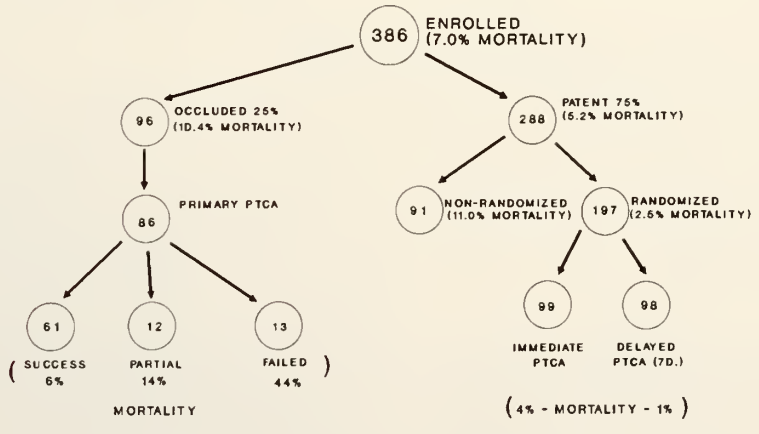
Immediate vs Delayed PTCA

The sequential strategy of thrombolytic therapy followed by immediate angioplasty in the early hours of acute myocardial infarction has been evaluated by three separate clinical studies involving close to 1,000 patients. The European Cooperative Study Group (ECSG) compared rt-PA alone to rt-PA plus immediate PTCA in 377 patients with acute myocardial infarction. Patients in the non-invasive arm of the trial had a more favorable clinical outcome with a lower incidence of recurrent ischemia during the first 24 hours (3% vs 17%), a significantly lower incidence of bleeding complications and a 14 day in-hospital mortality of 3% versus 7% in the invasive group. No differences between the treatment groups were observed in terms of infarct size or global left ventricular ejection fraction.

. . . immediate angioplasty did not improve clinical outcome or left ventricular function compared to delayed angioplasty in stable patients.

In the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) Trial, 386 patients received 150 mg of rt-PA in the early hours of acute myocardial infarction (Fig. 6). Seventy-five percent of the patients had a patent coronary artery at angiography 90 minutes later. Patients with a patent but severely stenotic vessel suitable for angioplasty were then randomized to immediate versus delayed angioplasty (performed 7 to 10 days later). At the time of hospital discharge neither group demonstrated a significant improvement in survival or left

Figure 6. **Results from the TAMI Trial**



ventricular ejection fraction. Bleeding complications and the need for emergent bypass surgery were more frequent among the patients who underwent immediate angioplasty. The incidence of reocclusion was similar in both groups, but the rate of crossover to emergency angioplasty for recurrent ischemia in the delayed group was 16%. Only 5% of the patients in the immediate PTCA group required repeat emergency angioplasty. Most importantly, 14% of patients in the delayed group demonstrated substantial reduction in the degree of stenosis at 7 days, and did not require angioplasty.

In the Thrombolysis In Myocardial Infarction (TIMI IIA) Trial patients were randomly assigned to immediate or deferred (18 to 48 hours post thrombolysis) angioplasty after receiving IV rt-PA for acute myocardial infarction. The results were similar to the TAMI trial. Immediate angioplasty was associated with significantly higher rates of emergent bypass surgery (19% vs 7%) and blood transfusions (26% vs 6%). No significant differences in survival or ejection fraction were observed between the two groups at the time of hospital discharge.

Thus, all three studies achieved similar results and reached the same conclusion that immediate angioplasty did not improve clinical outcome or left ventricular function compared to delayed angioplasty in stable patients. Furthermore, immediate angioplasty was associated with a higher risk of complications.

Rescue or Salvage PTCA

In the same TAMI I Trial cited above (Fig 6) 25% of the patients who received rt-PA for acute myocardial infarction demonstrated a persistently occluded infarct artery at angiography 90 minutes later. These patients all underwent immediate PTCA. Angioplasty was successful in 72%, partially successful in 14% (who were left with a high grade residual stenosis) and failed in 14% of the patients. There was a 29% in-hospital reocclusion rate despite therapy with heparin and antiplatelet agents. No significant improvement in regional or global left ventricular function was observed even among patients with successful angioplasty. Perhaps the most striking observation of this study, however, was the in-hospital mortality rate. Overall in-hospital mortality for this group of patients with an occluded artery following thrombolytic therapy was 14%. Patients in whom the infarct-related artery remained occluded even after rescue PTCA had an alarmingly high mortality of 44% in contrast to only a 6% mortality in patients in whom angioplasty of the persistently occluded artery was successful. In the absence of a suitable control group (patients with an occluded infarct-related artery who did not undergo immediate PTCA) it is difficult to draw a firm conclusion but the data suggests a significant survival advantage when rescue PTCA is successful, and an important disadvantage when it isn't successful.

Somewhat similar results were recently reported by Holmes and his colleagues at the Mayo Clinic who performed rescue PTCA on 34 patients with an occluded infarct-related artery after intravenous streptokinase therapy for acute myocardial infarction. Rescue PTCA successfully achieved infarct vessel patency in 71% of the patients, similar to that observed in the TAMI trial. The in-hospital mortality rate however, was much lower. It was 3% for the entire group and only 10% for those in whom angioplasty failed to reperfuse the occluded infarct-related artery. The improved survival in this study may have been related to the relatively high incidence (22%) of patients who underwent bypass surgery during their initial hospitalization. No significant improvement in ejection fraction was observed at the time of hospital discharge and in many cases the ejection fraction was actually worse. This may reflect the unavoidable time delay between initiation of thrombolytic therapy and subsequent coronary angioplasty (which averaged 5.0±1.3 hours in this study). Quite strikingly, during a mean follow up of 4 years, 89% of these patients remained alive and the majority of them were free of further myocardial infarction or the need for coronary artery bypass surgery. Thus this study demonstrated a significant long term survival advantage from rescue PTCA after failed thrombolytic therapy.

Reperfusion strategies continue to evolve as evidenced by the fifth Thrombolysis and Angioplasty In Myocardial Infarction Trial (TAMI V). This trial compared 3 thrombolytic drug regimens (rt-PA vs urokinase vs a combination of both of these agents) following which patients were randomized to either immediate catheterization within 90 minutes or deferred catheterization prior to discharge. Twenty-six percent of the patients in the deferred group crossed over to acute catheterization due to ongoing ischemic symptoms. *Selective rescue angioplasty* was used only in those patients who underwent immediate catheterization and who failed to reperfuse after

thrombolytic therapy. This approach differed from that of the previous TAMI and TIMI II trials in which angioplasty was performed only on a patent infarct-related artery.

Selective rescue angioplasty used synergistically with combination thrombolytic therapy achieved the highest reperfusion rates to date with vessel patency approaching 97%.

Combination thrombolytic therapy achieved one of the lowest reocclusion rates of any thrombolytic trial, only 2%. Recurrent ischemic symptoms were also less with combination therapy than with either of the individual therapies alone. In addition, combination therapy did not increase the risk of cerebral bleeding or other hemorraghic complication. The group that received immediate catheterization had significantly better regional wall motion, lower rates of in hospital events and no significant increase in bleeding complications. Selective rescue angioplasty used synergistically with combination thrombolytic therapy achieved the highest reperfusion rates to date with vessel patency approaching 97%.

Thus while rescue PTCA appears to impart a significant survival advantage for patients who fail to reperfuse following thrombolytic therapy these patients may be clinically difficult to identify. Some groups now advocate immediate angiography followed by elective rescue angioplasty only for those patients who demonstrate an occluded infarct related artery. Others reserve urgent catheterization for patients with persistent ST segment elevation, recurrent ischemia or ongoing hemodynamic instability within the first 24 hours following thrombolytic therapy. Further trials are necessary to help delineate which of these strategies is most clinically beneficial.

Delayed vs Elective PTCA

Since both immediate and delayed PTCA appear to offer no clear cut advantages to stable patients following thrombolytic therapy it is reasonable to question whether any strategy of routine angioplasty confers a significant benefit over and above a more conservative approach in which coronary angiography and subsequent PTCA are performed only for well recognized clinical indications. This question was directly addressed in the TIMI IIB trial (Fig. 7). In this trial more than 3000 patients received IV rt-PA for acute Q wave myocardial infarction and were then randomized to one of two groups. In the invasive group routine coronary angiography was performed 18 to 48 hours following thrombolytic therapy and prophylactic PTCA was then carried out if anatomically appropriate. In the more conservative group, coronary angiography and PTCA were performed only if patients developed spontaneous or exercise induced myocardial ischemia. PTCA was performed in 57% of the patients in the invasive arm of the trial, but was only required in 16% of the patients within the conservative group. Angioplasty success rates were high in both groups. At six weeks (42 days) follow up there were no significant differences in mortality, reinfarction rate or the need for bypass surgery between the two groups. More importantly at one year the mortality continued to be low with excellent survival rates for both groups.

Thus, these results indicate that the use of a conservative clinically driven approach to the post thrombolytic myocardial infarct patient which limits PTCA to those individuals with symptomatic or provokable ischemia is most appropriate. Based on these findings fewer than 1 in 6 patients will require invasive intervention.

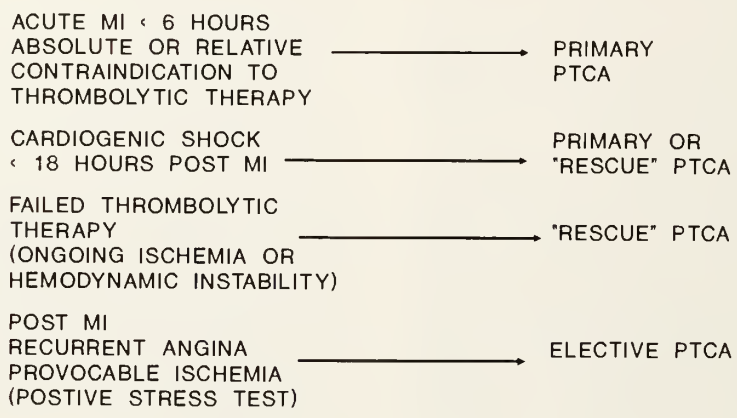
Conclusions

The role of coronary angioplasty in the management of patients with acute myocardial in-

Figure 7. **TIMI-IIB Trial Results**

	INVASIVE ARM DELAYED PTCA (N = 1636) (%)	CONSERVATIVE ARM ELECTIVE PTCA (N = 1626) (%)
PTCA DONE	57	16
SUCCESS	93	92
42D. FOLLOW-UP		
REINFARCTION	5.9	5.4
CABG	10.0	10.0
MORTALITY	5.2	4.7
ONE YEAR MORTALITY	7.0	7.6

Figure 8. **PTCA in Acute MI – Indications**



farction has undergone considerable evolution. Clear cut indications now exist (Fig 8). Primary or direct PTCA has been advocated for patients with absolute or relative contraindications to thrombolytic therapy. For those patients whose myocardial infarction has been complicated by cardiogenic shock, primary PTCA may be particularly beneficial offering a distinct survival advantage compared with other therapies. In addition, the optimal timing of PTCA may be extended beyond the usual 6 hour therapeutic window especially in those patients who are at increased risk from ongoing ischemia or hemodynamic instability.

Following thrombolytic therapy routine PTCA either immediate or deferred has no demonstrable benefits in stable patients and may be associated with an increased risk of complication. Rescue or salvage angioplasty may be appropriate for selected individuals in whom thrombolytic therapy fails to reperfuse the infarct-related artery. Because these patients and those who reocclude abruptly following successful thrombolysis may be difficult to identify clinically, all patients who receive thrombolytic therapy need to be monitored closely. Cardiac catheterization should be performed emergently for ongoing or recurrent ischemia. PTCA is indicated when the anatomy is suitable.

For patients who remain clinically stable following thrombolytic therapy, cardiac catheterization and elective angioplasty should be reserved only for those individuals who experience recurrent angina in the hospital or following discharge or who demonstrate provokable myocardial ischemia during exercise testing. This conservative, clinically oriented approach is particularly applicable to the majority of patients who experience acute myocardial infarction in the community hospital setting.

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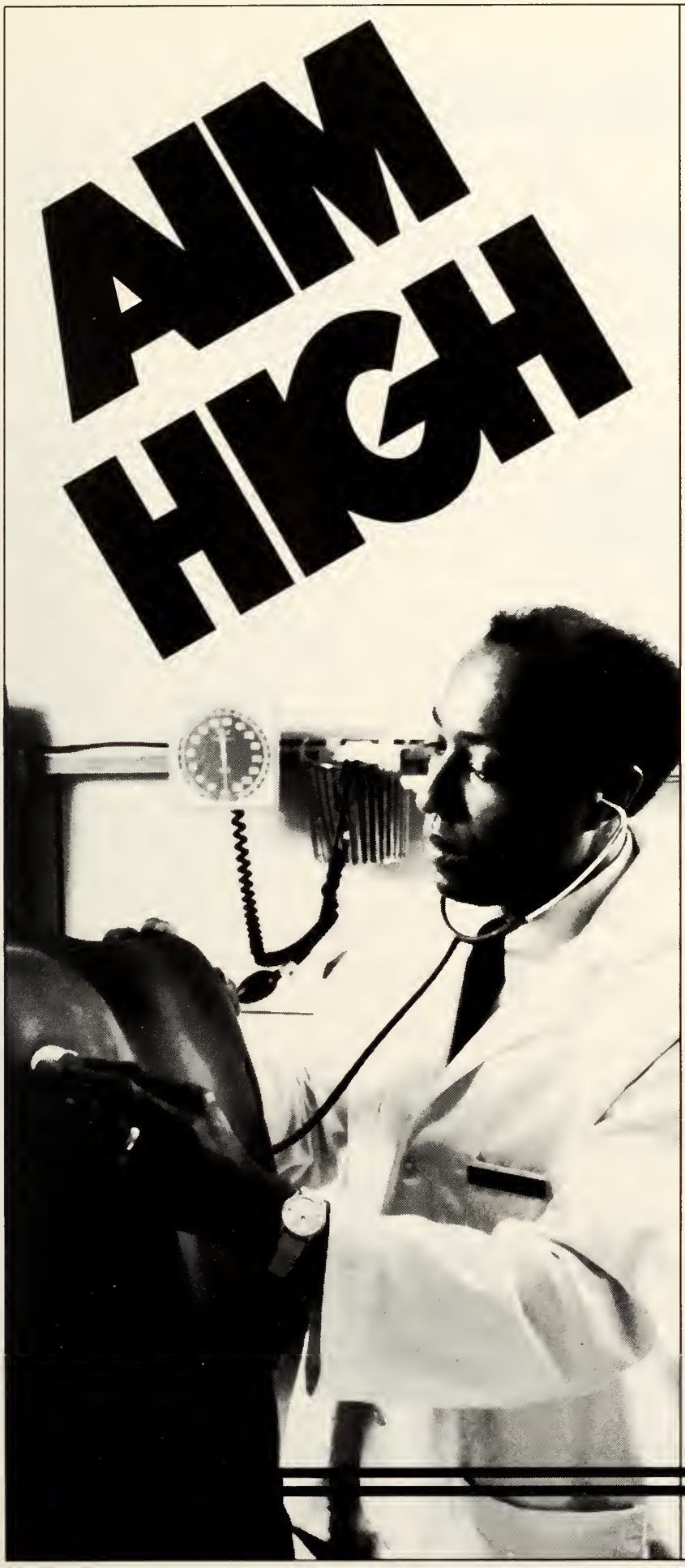
Address correspondence to:
Kenneth S. Korr, MD
Cardiac Catheterization Laboratory
The Miriam Hospital
164 Summit Avenue
Providence, RI 02906



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Utilization of Cardiac Catheterization Facilities

Heart disease is the leading cause of death in the nation as well as Rhode Island. In 1988, ischemic heart disease, commonly referred to as coronary artery disease, accounted for 2,614 deaths or 27% of all Rhode Island deaths, and 9,198 hospital discharges or 7% of all discharges from Rhode Island's short-stay hospitals.

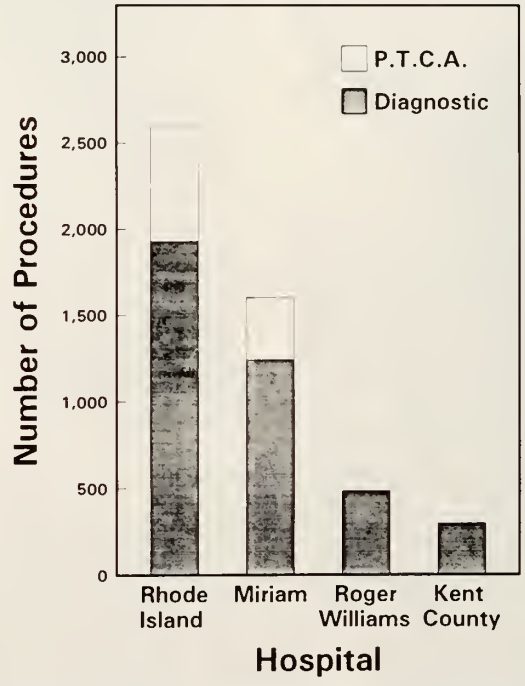
In Rhode Island, hospitals with cardiac catheterization laboratories perform invasive procedures for diagnosing and treating coronary artery disease. Coronary angiography and percutaneous transluminal coronary angioplasty (PTCA) are, respectively, the diagnostic and therapeutic procedures most commonly performed in these laboratories. The volume of procedures performed in cardiac catheterization laboratories are reported annually to the Rhode Island Department of Health, as recommended by the Cardiac Care Advisory Committee (CCAC).[1]

Presently, there are seven cardiac catheterization laboratories operating at four hospitals in Rhode Island: three at Rhode Island Hospital; two at Miriam Hospital; and one each at Roger Williams General Hospital and Kent County Memorial Hospital. As recommended by the CCAC, PTCAs are performed only at hospitals with open heart surgery programs, ie, Rhode Island Hospital and Miriam Hospital. Diagnostic cardiac catheterization procedures are performed at all four hospitals.

Figure 2 displays the volume of diagnostic cardiac catheterization procedures and PTCAs reported by hospital for 1990.[2] For procedures of all types, 52% were performed at Rhode Island Hospital, 32% at Miriam Hospital, 10% at Roger Williams and 6% at Kent County. During 1990, the cardiac catheterization facilities at Miriam and Kent County were operational for less than the entire twelve month period. Based on the CCAC's target range of 1100 to 1300 annual diagnostic cardiac catheterizations per room, statewide, the cardiac catheterization facilities were operating at between 80% and 68% of capacity in 1990.

Between 1982 and 1990, the

Figure 1. **Number of Cardiac Catheterization Procedures Performed, by Hospital and Type of Procedure, Rhode Island, 1990**



Submitted by the Office of Health Planning, Melinda L. Komiske, Chief. Health by Numbers *is edited by Jay S. Buechner, PhD, and William J. Waters, Jr., PhD.*

number of cardiac catheterizations performed in the state increased 220%, an average annual rate of 13% from 1464 to 3951 procedures, and PTCAs increased 915%, an average annual rate of 35% from 92 to 1026 procedures (Figure 2).

Since 1982, the rate of diagnostic cardiac catheterizations per 100,000 population in Rhode Island has been below the national rate; however, the percentage difference has been growing smaller. In 1982, the Rhode Island rate for diagnostic cardiac catheterizations was 76% of the US rate, rising to 88% of the national rate in 1989. In terms of the rate of PTCAs performed, in 1986, Rhode Island and the nation were identical; in 1989, Rhode Island's rate was 82% of the US rate for PTCAs (Figure 3).

Clearly, the utilization of cardiac catheterization services has grown rapidly during the 1980s. In the future the Department of Health, in conjunction with the Cardiac Care Advisory Committee, will continue to monitor this growth and to assess the adequacy of cardiac catheterization services for Rhode Island's population.

Figure 2. **Number of Cardiac Catheterization Procedures Performed, byYear and Type of Procedure, Rhode Island, 1982-1990**

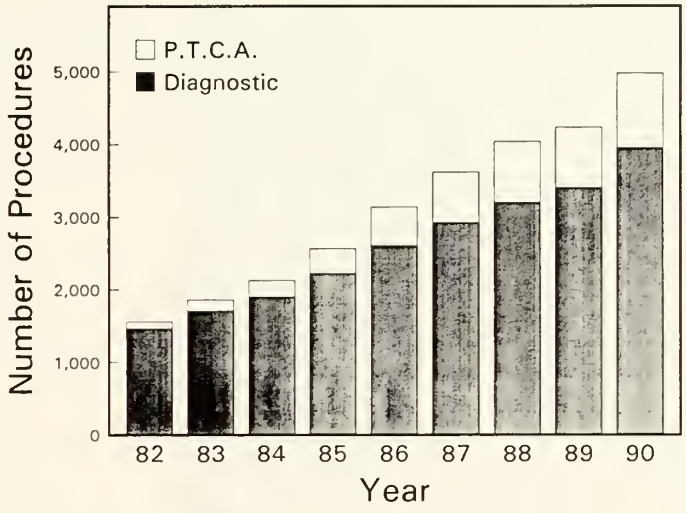
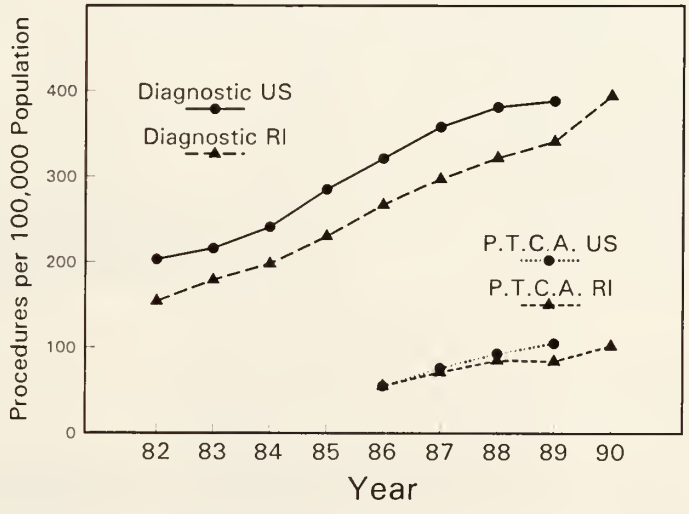


Figure 3. **Utilization Rate for Cardiac Catheterization Procedures, by Year and Type of Procedure, Rhode Island and United States, 1982-1990**



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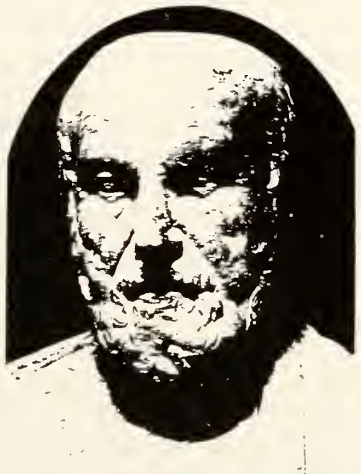
The Hippocratic Oath

James T. McIlwain, MD
Robert W. Hopkins, MD
Candace M. McNulty, MD
Herbert Constantine, MD
Alan B. Weitberg, MD
Steven M. Opal, MD
Louise S. Kiessling, MD
William Braden, MD
Richard A. Carleton, MD
Edward M. Beiser, PhD, JD

Periodically, the Journal has asked its readers to comment in writing on questions the answers to which are neither simple nor convincingly clear. The Hippocratic Oath, which most of us have taken, is now viewed by many physicians with increasing skepticism. Accordingly, the Journal invited ten persons to share their thoughts on the Oath, its meaning, its implications, its limitations. Is it a personal commitment not to be tampered with or is it an anachronism?



Hippocrates. Roman statue of the Hellenistic period. Fourth century B.C.

It is easy to be cynical about oaths because they are mere words and few really believe in their power to regulate human behavior. Indeed we tend to be more impressed by loud than by solemn swearing, so it is remarkable that vows are still extracted from those entering orders holy and profane. To understand this ritual we may look back to a time when, for our Anglo-Saxon forebears, swearing an oath (Old English *ath*) was serious business. *Athbryce* (oath-breach) had painful consequences and to be *athwyrthe* (oath-worthy) was to enjoy great advantage. The cornerstone of Anglo-Saxon legal procedure was the oath. Denial was stronger than accusation and usually, innocence was proved if the oath of the accused was supported by the oaths of a sufficient number of *athwyrthe* witnesses. Not so for the known perjurer, though. When he or she came before the court, the "proof" went to the accuser, who had but to swear a good and attested oath for guilt to be established.

Oaths reflected not only the values but also the political, social and perhaps even the personal preoccupations of those who impose them. The Hippocratic Oath appears to be no exception. It requires, for instance, that physicians distance themselves from surgeons and from those who neglect the financial needs of their teachers. One can well imagine this having been written by a penurious professor of physick; but, according to the experts, he was not Hippocrates, who apparently was a gifted surgeon. In any case, it is clear that most physicians of our day conveniently ignore these and other awkward strictures of the Hippocratic Oath, if not in the operating room, then certainly when turning a deaf ear to the dunnings of their medical schools.

Local efforts at reform have produced the Physician's Oath, composed largely by Brown's MD Class of 1975 and repeated annually by a chorus of graduating medical students. This pledge improves on the Hippocratic Oath but still reflects the preoccupation of its creators. One sentence reads "I will not permit consideration of race, gender, sexual preference, religion, nationality or social standing to come between me and my duty to anyone in need of my services." This fashionable litany recalls a host of laws and pious declarations but seems to add little to the core obligation of the old oath,

I will use treatment to help the sick according to my ability and judgment,

or that of the new,

The health and dignity of my patient will ever be my first concern.

James T. McIlwain, MD
Professor of Medical Science
Brown University

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The question of the relevancy of the Hippocratic Oath has, I think, two parts: should physicians take any oath, and if so, should it be the Hippocratic Oath?

The first question is the appropriateness of oaths in general and specifically oaths for medical graduates. There are appropriate legally binding oaths, such as those required of witnesses prior to giving legal testimony. Violation of the oath under these circumstances is perjury, with attendant penalties. Other oaths, including ours, are largely ceremonial. These are taken as part of a ceremony which recognizes the undertaking of an important social commitment, such as an oath of office taken by a public official. Such oaths are generally not legally binding *per se* but rather are a public admission of one's intent to function properly in the chosen position. In general, society has a right to expect proper performance from anyone undertaking activity which has such a direct effect on the welfare of others as medicine. For this, an oath is not necessary, nor is there evidence that those taking such an oath perform differently from those who do not.

In the sense of a formal public commitment, the Hippocratic Oath taken literally is obviously inappropriate for the times. Swearing "by Apollo, by Asclepius, by Hygeia, by Panacea and by all the gods and goddesses" may not suit the religious convictions of today's medical graduates. Those of us who "use the knife" go through the same educational process and graduation ceremonies and presumably take the same oaths as those who do not. Although few today would literally "give a woman pessary to cause abortion," today's safe and legal abortions are clearly within the province of well trained medical graduates. These and some other components of the Oath are no longer applicable. On the other hand, the Hippocratic Oath is truly an extraordinary historic document which includes important timeless and accepted principles, and much of it does remain appropriate.

Should it be an integral part of graduation ceremonies today? If used in an historic sense as a recognition of the remarkable accomplishments and wisdom of those who have preceded us–I see no reasons why it should not be a part of the ritual which celebrates the transition from student to physician. Unfortunately, some political/religious groups have used selected segments of the Hippocratic Oath to malign physicians whose activities offend their beliefs and do not concur with outmoded sections of the Oath. It may be more appropriate, therefore, for students themselves to think seriously about their future roles and to develop (as has been done at Brown) their own Collective Statement, although I personally prefer not to consider it an "oath".

In summary then, I do not think medical graduates should be required to take any oath. As part of graduation ceremonies, however, I think it reasonable to use the Hippocratic Oath as a reference to the historic and noble traditions of our profession – but not as an oath entirely applicable today. A possibly better alternative is for students to adopt their own Collective Statement.

Robert W. Hopkins, MD
Department of Surgery
The Miriam Hospital

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Traditionally, a requirement of many medical schools has been that medical students upon graduation take the oath of Hippocrates. This ancient oath has been utilized by American medicine since the eighteenth century. Given the increasing complexity of the practice of medicine as well as the striking changes in the lifestyle and culture of Americans, it becomes reasonable to ask whether this oath is still relevant to today's physician. The oath of Hippocrates is a series of pledges emphasizing respect for one's teachers, the sharing of one's knowledge with colleagues and students, care of the ill to the best of one's ability, the absence of malicious intent in the practice of medicine, avoidance of conscious harm to patients, patient confidentiality, and adherence to the highest standards in both professional and personal conduct and thought. I, personally, find these aspects of the Hippocratic Oath quite appealing and useful. They are reminders and guidelines of my responsibility as a physician to my patients. The practice of medicine has dramatically changed in the last twenty years. No longer is it a relationship between just two people: the physician and the patient. Both the traditional physician-patient relationship and the practice of medicine continue to be redefined by the Government, medical health insurance companies, patients' employers and patients themselves. All of these do not necessarily indicate bad changes but they certainly have altered the role of physicians in patient care. However, the responsibility and ethics of physicians remain the same. The Hippocratic Oath continues to be very important in this area; it serves as a reminder that we, as physicians, are increasingly the only advocate of the patient and that our primary responsibility is to provide the best medical care we can.

In spite of this, there are two outstanding (and what I view as major) flaws in the Hippocratic Oath. Both involve women. The first is that the oath specifically addresses only men, and by doing so, excludes women. Certainly, this was understandable in the past when there were no women physicians. However, that changed in 1970 when the Equal Opportunities Act was adopted by the Assembly of American Medical Colleges. In that year, the percentage of women in medical schools increased from 6 to 9.1% and rose to 34.2% by 1986. By the year 2000, 20% of all physicians will be women.

The second deficiency is the pledge "not to cause abortion." Although the abortion issue has recently been associated with controversy, it was widely used in the United States in the 19th century as a means of limiting family size. After the Civil War, most states passed statutes making abortion illegal. Two reasons were cited: one was concern about declining birth rates in the country and the other was the Hippocratic Oath by the American Medical Association. Abortions at that time were usually performed by female midwives; this group was also viewed by physicians as a rival in health care. These statutes effectively put midwives out of business and benefited physicians in a concrete way. Although illegal, abortions continued to be performed during the 20th century. The number and rate varied often increasing during downturns of the economy such as the Depression. Abortion, fortunately, again became a legal option in 1973 when the Supreme Court ruled on Roe vs Wade. No one can force a physician to perform an abortion. But it is also true that no one, including physicians, have the right to control a woman's body or her decision to have an abortion. That decision and control are hers alone.

Regarding the original question "Does the Hippocratic Oath have relevance to today's physicians?", I would rephrase it to "Am I or rather, are women, both as physicians and patients, relevant to the Hippocratic oath?" In its current male-oriented form, I think not. Could the oath be changed and updated to reflect and include all persons? After all, Hippocrates did not write the oath, and it has been modified in the past. It think that it is time to do so again.

Candace Miklozek McNulty, MD
Director, Doppler-Echocardiac Laboratory
The Memorial Hospital

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I distinctly remember taking the Hippocratic oath. We stood, the medical graduates, on a sunny Sunday, in front of the Lockwood Memorial Library at the University of Buffalo, full of success, and took the Oath. It was full of pageantry, noted and enjoyed by relatives and friends. After all, the Law graduates had nothing like it. I remember explaining to an uncle that it wasn't legally binding. He seemed surprised.

Did the oath make me more honest or moral? I don't think so. My father, who wouldn't cheat on buying a five-cent newspaper (the price at the time) made me honest. In a like manner I think physicians must be receptors of honesty and morality to our student offspring every day of their medical school education. I find that our medical students are basically honest and moral. I believe that as students

learn the professional role as confidants of their patients, and, as we teach them the powerful pharmacological and surgical tools that society allows them to wield in the service of their patients, that we the teachers must provide constant examples of moral rectitude. We can't depend on the archaic Oath to do it for us.

I have participated in many discussions around the question of to whom physicians are responsible, eg, to the individual, the community, the society in general, or perhaps to a Higher Power. I am bemused by these discussions. I have always had the perhaps eccentric belief that the physician owes an overriding responsibility for honesty and morality primarily to the individual patient standing in front of him or her at any given moment. If we are going to have an oath then let the doctor take it for each patient. It might be like a reverse consent form. A reminder lest we forget the purpose of our profession.

Recently it has become fashionable to update the Oath. I am not sure that this makes any difference. The original Hippocratic Oath was taken in ancient times in a religious context. Since taking the Oath is essentially now pageantry, the original form at least reminds us of the issues that concerned our forerunners. Commitment to the good of the patient is a timeless virtue. I don't know how it worked on the island of Cos but we should teach its precepts daily and not hope for it as a godsend on graduation day. I bet it didn't work that way for the Greeks either.

If we must continue to administer the Oath, I then suggest it would be more appropriate if we required it on the first day of medical school, not the last.

Herbert Constantine, MD
Department of Medicine
Rhode Island Hospital

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Is the Hippocratic Oath relevant to the practice of medicine today? It definitely is and certainly is not.

Webster defines an oath as "a solemn formal calling upon God or a god to witness the truth of what one says or to witness to the fact that one sincerely intends to do what one says." In the 5th and early 4th centuries BC, when medicine was emerging from an age of mysticism and lacking in any sociopolitical structure, the oath served a functional purpose. Those adhering to it were members of a medical "society" who proffered their skills as art; even to the extent that surgery was recognized as a separate discipline.

Yet the main points of the oath, caring for and teaching one's colleagues and their families, doing no harm (*primum non nocere*, here referring to suicide and abortion), separating medical from surgical approaches to care, maintaining patient confidentiality and adhering to high moral and ethical standards, have been woven into the fabric of modern medical practices to varying degrees.

Patient confidentiality and the need for medical ethicism have survived without a doubt. Caring of one's colleagues without fee or stipulation is practiced haphazardly and it is my observation that in this gesture was a tenet of previous generations, now less popular among our younger colleagues. Both suicide and abortions were condoned or advised by ancient Greeks, but Hippocrates, under the influence of Pythagoros, condemned these practices according to their personal socioreligious principle within the broadest (or narrowest) interpretation of the law.

And so several of the principles of this oath, primarily relating to the art of medicine, live today perhaps tacitly attributed to Hippocrates (perhaps not). But the oath itself is irrelevant. It is not administered as an oath, most of us scarcely remember its specifics and today's medical graduates would be hard pressed to recite it. And certainly the sections on suicide and abortion do not have broad appeal, one way or the other.

The Hippocratic Oath is an important document for understanding why we, as physicians, act in some of the ways that we do. For this reason, it deserves to be read, if not studied. But as an oath, it lacks credibility in its entirety; parts of it now are nothing more than medical historical curiosities. Perhaps it is time for a new delineation of the principles of our art, to be read, studied and practiced by generations of physicians to come. For as Hippocrates undeniably wrote those many centuries ago. "Life is short and the art long; the occasion fleeting; experience fallacious and judgment difficult."

Alan B. Weitberg, MD
Interim Chairman of Medicine for Clinical Services
Roger Williams Medical Center

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I am a great believer and staunch supporter of the honor and tradition of our beloved profession. The practice of medicine, by its very nature, is a unique way of life which requires the utmost in moral standards and ethical conduct. We are entrusted by our patients to care for them when they are most vulnerable and we have a moral imperative to uphold our long-standing tradition of caring and sacrifice. To many physicians, the 2,500 year old Hippocratic Oath represents an affirmation of this historical trust which is bestowed upon us when we graduate from medical school. While the Hippocratic Oath contains many of the basic tenets upon which our profession is based, I now find many of its passages to be irrelevant and at time inappropriate.

The first part of the Hippocratic Oath is filled with excessive gratitude and indebtedness to the physician's teacher. The Oath states "... To hold my teacher in this art equal to my own parents; to make him partner in my livelihood; when he is in need of money to share mine with him; to consider his family as my own brothers." While this level of gratitude may have been highly laudable and acceptable in antiquity, no such adulation is apparent or appropriate today. Physicians of the past once learned their trade as apprentices to a single or few learned clinician-teachers. In modern medicine literally hundreds of educators participate at various steps in the development and training of a medical student. Medical students should certainly express their appreciation upon graduating from medical school; yet, they should not feel eternally indentured to the numerous physicians and medical educators who contributed in their training.

Additionally, like most physicians, I disagree with the Hippocratic Oath's prohibition of abortion. I believe it is both proper and ethical to perform an abortion when a pregnancy places a woman's life at stake.

Some physicians contend that the Hippocratic Oath should be viewed as a metaphor. Perhaps the Oath should not be interpreted literally, but simply accepted for some of the principles described in it. Others argue that the Hippocratic Oath links us to the fraternity of physicians of the past and present. I respectfully disagree. I do not believe the Hippocratic Oath is immutable or permanently transfixed to medical graduation ceremonies.

When I graduated from medical school, my classmates and I were given the option to recite the Hippocratic Oath or the Prayer of Maimonides at our graduation ceremonies. We overwhelmingly chose "the Prayer" over "the Oath". If given the choice today, I would again vote for the Prayer of Maimonides as a more fitting tribute to our profession. The abbreviated Prayer of Maimonides is as follows:

"Almighty God, Thou hast created the human body with infinite wisdom. Thou has blessed Thine earth, Thy rivers and Thy mountains with healing substances; they enable Thy creatures to alleviate their sufferings and to heal their illnesses. Thou has endowed man with the wisdom to relieve the suffering of his brother, to recognize his disorders, to extract the healing substances, to discover Thy powers and to prepare and to apply them to suit every ill. In Thine eternal providence Thou hast chosen me to watch over the life and health of Thy creatures. I am now about to apply myself to the duties of my profession. Support me, almighty God, in these great labors that they may benefit mankind, for without Thy help not even the least thing will succeed.

Inspire me with love for my art and for Thy creatures. Do not allow thirst for profit, ambition for renown and admiration, to interfere with my profession, for these are the enemies of truth and of love for mankind and they can lead astray in the great task of tending to the welfare of Thy creatures. Preserve the strength of my body and of my soul that they ever be ready cheerfully to help and to support rich and poor, good and bad, enemy as well as friend. In the sufferer let me see only the human being. Illumine my mind that it recognizes what presents itself in that it may comprehend what is hidden or absent. Let me not fail to see what is visible, but do not permit it to arrogate to itself the power to see what cannot be seen, for delicate and infinite are the bounds of Thy great art for caring for the lives and the heath of Thy creatures. Let me never be absent minded. May no strange thoughts divert my attention from the bedside of the sick, or disturb my mind in its silent labors, for great and sacred are the thoughtful deliberations required to preserve the lives and the health of Thy creatures.

Let me be content in everything except in the great science of my profession. Never allow the thought to rise in me that I have attained sufficient knowledge, but vouchsafe to me the strength,

the leisure and the ambition ever to extend my knowledge. For our art is great, but the mind of man is ever expanding.

Almighty God! Thou hast chosen me in Thy mercy to watch over the life and death of Thy creatures. I now apply myself to my profession. Support me in this great task that I may benefit mankind, for without Thy help not even the least thing will succeed."

Steven M. Opal, MD
Infectious Disease Division
The Memorial Hospital

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The 2,500 year old Hippocratic Oath seems of limited usefulness. Its relevancy today is based on some enduring concept, but I have major concerns with some of its specific elements. Since there are many versions of the ancient oath as well as modern modifications, it appears that even in early Greek times there was some variability as to what was sworn to. I've come upon three somewhat different translations in a brief review.

Having an oath is a good idea. It sets forth a series of general principles that the profession should be able to agree upon. It reinforces the importance of high personal moral and ethical standards.

In favor of the oath is the concept of continuity of the profession, the admonition to pass on the skills, the art and science from one generation to another. There is continuity of a tradition in addition to continuity of knowledge and treatment. One of the prime tenets of the Hippocratic Oath that is as relevant today as it was when the original was composed is the admonition that one is to help the sick with treatment in accordance to one's own ability and judgment, but never with a view to causing harm. In other words, codification of the concept "do no harm".

Another cornerstone of the oath, is the concept of confidentiality between physician and patient. This concept goes to the core of one of the major controversies in health care today, the issue of trust. It is significant that a large component of the oath deals with this issue of confidentiality. To quote "And whatsoever I shall see or hear in the course of my profession. . . I will never divulge, beholding such things to be holy secrets." This is a major responsibility and it is important to be reminded of it.

Broadly this is an oath to a higher principle and with our diverse society today, calling upon the gods and goddesses of Ancient Greece is an anachronism. The modern versions deal with this more appropriately.

One of my major difficulties with this oath is its oath of allegiance to a masculine guild. Physicians in ancient times were a guild where the teacher took on apprentices and where the apprentice after a period of time, went out into practice and repeated the process. But these were clearly males directed "to impart precept, oral instruction, and all other instruction to my own sons, the sons of my teacher . . ." This is a very uncomfortable concept for a woman physician. Since approximately 30% of physicians today are women and the percentage is rising, this is not an acceptable form of oath.

Another major concern also deals with women, namely, the fact that the oath proscribes any form of abortion. The controversy over abortion is very real in this country. Including in the physicians oath a total negation of all concepts of abortion is not appropriate for our society's norms today. Other people might have the same objection with the segment of the oath that forsakes any form of assisted suicide. The concept of assisted suicide has still greater potential for abuse than abortion, in my view, and it is an important open ethical issue.

An oath is appropriate but one of the modified forms such as that developed and used by the Brown Program in Medicine classes for some years is more appropriate today. The point behind the oath is to emphasize to new physicians and old, both their responsibilities and the principles behind their profession. These need to be articulated in a way that maintains their universality rather than stated in a manner confined to the particular mores of a specific time.

Louise S. Kiessling, MD
Chief, Department of Pediatrics
The Memorial Hospital

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It seems almost unthinkable to try to alter or do away with the Hippocratic Oath. After all, what would we replace it with? The vision that comes to mind is of a committee, deadlocked on the important points, finally producing an ethical statement so filled with detail, so bland, as to excite neither controversy nor feeling.

To be sure the Oath is quaint and out of date, to the degree that we hardly take its details seriously. Swear by all the gods and goddesses? Teach my sons, and not my daughters? Not do surgery? "Get real." the graduating medical student might say. But these are quibbles. We don't expect an Oath put forth thousands of years ago to conform to our comprehension of medicine today. We look to it for timeless principles, which we ourselves will apply to modern options like respirators or in vitro fertilization.

And do we find such principles in the "Oath? Certainly. If I may paraphrase freely, the Oath tells us that learning is a debt, to be paid back by later teaching; that knowledge should be shared only with those who accept the accompanying responsibilities; above all, that knowledge is to be used only to help, not to harm; and finally, that as patients and their families entrust us with their secrets, the privacy of their homes, and their persons, these must be respected absolutely. What I cannot paraphrase is the sentence, "I will keep pure and holy both my life and my art." The author of the Oath says that medicine is more than just a job: it is a calling, which is to transform our lives, whether we are at the clinic or not.

There remains the challenge of adapting these principles to the factual realities of medicine today. Most of us still agree that we shouldn't be giving poison–but sometimes we should be turning off the respirator–and so forth. The development of such policies will require debate within the medical community as well as dialogue with the larger society. Most of us would prefer that society trust us to make the actual decision, rather than bind us with relatively inflexible statutes and courtroom declarations. Yet as we look to the larger society, we see ourselves reflected, sometimes as the pure and holy practitioners of the Oath, sometimes as just another crew of rapacious businessmen. Mostly this seems unfair, but occasionally all too true. If we want to keep our autonomy, the trust of society, our "reputation among all men", then the political process will not suffice. More than anything, these things will depend on physicians' daily acts of ethical courage and dedication.

William Braden, MD
Psychiatric Physician Consultants of Rhode Island

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The Oath of Hippocrates bears the dignity of many centuries of use. Living documents, such as the US Constitution, evolve. The Oath of Hippocrates has not evolved, has served its purpose and is now a dead document. It fully deserves enshrinement in a revered place in the history of medicine.

In what ways has it failed to meet the needs of modern medicine? They are many. This document fails to recognize the evolution of the medical profession. Today, many medical schools have nearly 50% representation of the female gender in its scholastic body; the oath speaks in the masculine. Generations of physicians have sworn to make teachers partners in their livelihood, to share money with teachers, to teach the family of teachers without cost – in this era of escalating tuition costs, costs from which families of teachers are certainly not immune, this is an unattained ideal. While the abortion issue finds the national and world society divided, certainly many, many physicians driven by modern social and humanitarian concerns, have caused abortion. Finally, how can one, in this era "swear by Apollo Physician, by Asclepius, by Health, by Panacea and by all the gods and goddesses . . .", long forgotten dignitaries and deities?

At the same time, the Oath has strengths. To swear to use treatment to help the sick according to the ability and judgment of the physician is unassailable. (Yet, the need for those decisions by health professionals, patients, and family to withhold care when death prolongation and not life improvement is the issue needs consideration.) One cannot quarrel with the pledge not to administer poisons (Are cytotoxic chemotherapy agents poisons?). The Oath recognizes special abilities: Board certification of surgeons and a steadily increasing array of increasingly narrow superspecialists is a logical sequel. Abstention from intentional wrong-doing, abuse of the bodies of human beings, and abridging scrupulous confidentiality are as important today as in centuries past.

Should not a modern Oath be created? Should it not continue to include a commitment to the care of the ill? Should it not expand and incorporate concepts of disease prevention? Should it not

incorporate a commitment to ongoing study in an area of explosively expanding information? Should it not include a commitment to prioritize those things which improve the quality of life? Should it not include a commitment to the delivering of care to the needy without regard for recompense?

The Oath served our forbearers well. The Oath, unlike the constitution of democratic nations, had no mechanism for remaining modern and relevant. A pledge to the historical principles of the medical profession is appropriate; a new oath to guide the physicians of the 21st century is needed.

Richard A. Carleton, MD
Physician-in-Chief
The Memorial Hospital

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Earlier this semester, while conducting a seminar in medical ethics for a group of students in Brown's Program in Liberal Medical Education (PLME), I encountered a phenomenon which has by now become almost routine. I had presented a case for students to consider, and was pressing one student with a series of examples of physician misconduct.

"But why is such conduct unacceptable?" I asked. The student played his trump card: "Because it violates the Hippocratic Oath."

To which I responded: "Have you ever read the Hippocratic Oath?" After hearing the anticipated negative answer, I administered the *coup de grace*: "Suppose I tell you that Brown University does not utilize the Hippocratic Oath at graduation. Rather, we use an oath written by Brown medical students approximately 20 years ago." (I did not tell this student that many, if not most, Brown medical students see that oath for the first time as they are about to receive their MD degree.)

The student's intuition was typical of others in his position, and I expect, of many practitioners who can at best dimly remember what they swore to uphold as they graduated from medical school: whatever strikes one's "gut" as beyond the pale, must be prohibited by the Hippocratic Oath. (The exact equivalent in the world of politics is the citizen who says: "This must be unconstitutional," meaning: "I don't like this.")

To my knowledge those receiving the MD degree are the only graduates of whom Brown expects an oath. Graduate students receiving the PhD or the MA are not asked to pledge much of anything; nor are the undergraduates. (Brown has no other professional schools, neither a law school nor a business school.)

To be sure, the Oath subscribed to at the medical school ceremony can be viewed as part of the pageantry, not meant to be of substantive import. Be that as it may, I suggest that the matter of oaths speaks to a vital question: To what extent, and precisely, in what particulars, is the profession of medicine to be understood as significantly distinct and different from other professions, occupations, and trades?

The text of the Hippocratic Oath is appended to this article, along with the current text of the Oath utilized at Brown. One notes immediately that the two oaths appeal to radically different sources of authority. The Hippocratic Oath appeals to a panoply of pagan deities: "I swear by Apollo Physician, by Asclepius, by Health, by Panacea, and by all the gods and goddesses, making them my witness." Recognizing the full range of religious beliefs (or lack thereof) represented in the medical profession, one can state with reasonable confidence that virtually no physician or medical student bases his or her notions of moral obligation on these gods. Insofar as aspects of the Hippocratic oath are thought to be relevant to defining the ethical content of contemporary medicine, it must be because those provisions can be justified on some independent basis.

The Brown Oath does not seek to substitute a contemporary set of religious authorities. Rather, it bases the physician's ethical obligations on other norms of the profession:

> "Now being admitted to the high calling of the physician . . ."
> "In the spirit of those who have inspired and taught me . . . (I pledge) to promote all that is worthy in the ancient and honorable profession of medicine."

Why is medicine a "high calling"? Is it a higher calling than engineering, or architecture, or biological research, or painting? Of all the activities engaged in by modern physicians, are some "higher" than others? Is neurosurgery a higher calling than primary care pediatrics? Is the plastic surgeon who limits

his or her practice to the most difficult burn victims engaged in a higher calling than the plastic surgeon who makes a fortune doing "nose jobs"?

In sum, the Brown Oath is based on the graduate's pledge to do "all that is worthy." It provides very little guidance to determine just what that pledge includes.

The Hippocratic Oath's appeal to the enumerated pagan gods need not be viewed as simply a quaint symbolic usage. It may be understood to assert a normative basis indeed, a shared normative basis. The Brown student on the other hand, is directed not to religious authority, but rather to "the spirit of those who have inspired me . . ." Notice the tautology: the new physician is to measure his or her ethical conduct by comparison with role models; but how does he or she recognize "those who have inspired me" without reference to explicit normative standards?

One of the most quoted lines in all of American constitutional law is Justice Stewart's famous discussion of the definition of obscenity: It may be hard to provide a comprehensive definition, but "every red-blooded American" will recognize it when he sees it.

The "I'll know it when I see it" school of medical ethics is not intellectually compelling. This is not to particularly criticize the authors of the Brown Oath. Rather, it is to recognize and to call attention to the fact that the paradigm of medical ethics which made sense to the ancient Greeks is not available to most moderns. So we settle for second best: learn by example from those whom you respect. To which we may add: be careful and self-conscious as to your choices of whose role to emulate.

The final paragraph of the Brown Oath does seek to provide ethical content. It does so by adopting an explicitly patient-centered ethic:

> *"The health and dignity of my patient will ever be my first concern . . . I will not permit considerations of race, gender, sexual preference, religion, nationality or social standing to come between me and anyone needing my services."*

To be sure the Oath is singularly unhelpful in informing the physician as to what constitutes "health and dignity". The patient's preferences? The patient's family's concerns? The physician's own values? The values of those who established a particular medical school, hospital, HMO, or primary care clinic?

Each of the oaths contains some substantive content. Interestingly, the closest fit appears to be respect for confidentiality. The formulation in the Hippocratic Oath is the longer of the two:

> *"And whatsoever I shall see or hear in the course of my profession as well as outside my profession, in my intercourse with men, if it be what should not be published abroad, I will never divulge, holding such things to be holy secrets."*

Brown's version is more succinct:

> *"I will hold in confidence all that my patient relates to me."*

The significant difference between the two is not their length. Rather, the Hippocratic Oath explicitly limits confidentiality to that which "should not be published abroad." The modern (Brown) version does not distinguish between what should be secret and what shouldn't. It imposes a universal norm of confidentiality upon "All that my patient related to me". One would need to know whether the ancient Greeks had a sufficiently common definition of the things which deserved confidentiality, or whether this was controversial at the time. One need not know a great deal about modern medicine to recognize that an oath to "hold in confidence all that my patient relates to me" cannot possibly be an absolute norm.

The Hippocratic pledge to "use treatment to help the sick according to my ability and judgment, but never with a view to injury and wrong doing," resonates positively to the modern ear. But the sentences which follow immediately present ancient conclusion to issues which are very much with us today:

> *"Neither will I administer poison to anybody when asked to do so, nor will I suggest such a course. Similarly, I will not give a woman a pessary to cause abortion. But I will keep pure and holy both my life and my art."*

The modern medical student might well ask whether and why the physician's life should be more "pure and holy" than anyone else's. Indeed, many if not most medical students might argue that the definition of a "pure and holy life" is private, and is so variable in our society as to provide no real guidance.

It is difficult to imagine two issues in the current medical scene which engender more ethical controversy than the two just quoted to which the Hippocratic Oath provides absolute prohibitions: never administer a poison; no abortions.

The Hippocratic Oath includes obligations which are indeed alien to our modern sensibilities:

"I swear to hold my teacher in this art equal to my own parents; to make him partner in my livelihood; when he is in need of money to share mine with him; to consider his family as my own brothers, and to teach them this art, if they want to learn it, without fee or indenture; to impart precepts, oral instruction, and all other instruction to my own sons, the sons of my teacher, and to indentured pupils who have taken the physician's oath, but to nobody else."

What emerges from this text is the sense of a closed guild, of a fraternity, motivated in part by norms of that culture (one owes to one's teacher that which one owes to one's parents) and in part by considerations of economic advantage. Certainly contemporary notions of anti-trust would be offended. Of course, organized medicine and its specialized subgroups have been accused in much more modern times of seeking to limit the number of physicians who might compete in the market place.

In addition, one notes the "quaint" (still only quaint?) references to sons, to the total exclusion of women.

These components of the Hippocratic Oath clearly alert us to the context in which it was written, and in which it was subscribed to. This leaves, then, a fundamental question: Are the norms of ethical medicine best understood as restricted to a particular time and place? In the alternative, are there some norms of ethical medicine which can properly be asserted to be universal, as in "We hold these truths to be self-evident"?

One distinctive feature of the Brown Oath is the extent to which it defines a physician's obligation by reference to the needs of the patient. The language of the oath is sweeping, so sweeping that it provides little by way of guidance. One can admire a dedication of the physician's life to "the care of the sick and the promotion of health and the service of humanity."

Of even broader scope is the "duty to anyone in need of my services." Certainly there must be important limitation to the extent to which the needs of "anyone"–of all "of humanity" can define the behavior of an ethical physician.

Should medical schools reconsider the use of the Hippocratic Oath, if that is what they use? Should they substitute a modern version, and if they choose to do so, is the Brown Oath an improvement? Clearly no text which can be printed on half a page can be expected to define all of medical ethics. The starting point of a constructive effort would not be close textual revision. The most important question raised by the design of an oath is whether, and why, and in what respects, the profession of medicine is special and distinctive.

Edward M. Beiser, PhD, JD
Associate Dean of Medicine
Brown University

The Hippocratic Oath

I swear by Apollo Physician, by Asclepius, by Health, by Panacea and by all the gods and goddesses, making them my witnesses, that I will carry out, according to my ability and judgment, this oath and this indenture. To hold my teacher in this art equal to my own parents; to make him partner in my livelihood; when he is in need of money to share mine with him; to consider his family as my own brothers, and to teach them this art if they want to learn it, without fee or indenture; to impart precept, oral instruction, and all other instruction to my own sons, the sons of my teacher, and to indentured pupils who have taken the physician's oath, but to nobody else. I will use treatment to help the sick according to my ability and judgment, but never with a view to injury and wrongdoing. Neither will I administer a polson to anybody when asked to do so, nor will I suggest such a course. Similarly I will not give a woman a pessary to cause abortion. But I will keep pure and holy both my life and my art. I will not use the knife, not even, verily, on sufferers from stone, but I will give place to such as are craftsmen therein. Into whatsoever houses I enter, I will enter to help the sick, and i will abstain from all intentional wrongdoing and harm, especially from abusing the bodies of man or woman, bond or free. And whatsoever I shall see or hear in the course of my profession, as well as outside my profession in my intercourse with men, if it be what should not be published abroad, I will never divulge, holding such things to be holy secrets. Now if I carry out this oath, and break it not, may I gain forever reputation among all men for my life and for my art; but if I transgress it and forswear myself, may the opposite befall me.

Physician's Oath

Now being admitted to the high calling of the physician, I solemnly pledge to dedicate my life to the care of the sick, the promotion of health and the service of humanity.

In the service of those who have inspired and taught me, I will seek constantly to grow in knowledge, understanding, and skill and will work with my colleagues to promote all that is worthy in the ancient and honorable profession of medicine.

The health and dignity of my patient will ever be my first concern. I will hold in confidence all that my patient relates to me. I will not permit consideration of race, gender, sexual preference, religion, nationality or social standing to come between me and my duty to anyone in need of my services. This pledge I make freely and upon my honor.

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THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

Ninety Years Ago
(November, 1901)

Jay Perkins, MD writes a closely reasoned, lengthy essay entitled, A State Sanatorium for Tuberculosis in Rhode Island. What Would It Accomplish? The author first etiologically distinguishes between a sanitarium and a sanatorium. The former, he points out, is a term reserved for open health resorts while the latter, based upon the root *sanare* (to heal) is an institution for the express purpose of curing disease. Historically, sanatoria are establishments designed to facilitate healing of disease, especially "parasitic diseases" such as tuberculosis.

Perkins determined that there were 1,009 deaths from tuberculosis in the state of Rhode Island during the preceding year (1900). Of these 850 were pulmonic (ie consumptive). Under the assumption that there are three active cases of tuberculosis for each tuberculous death, he calculates that there are at least 2,550 consumptives in Rhode Island without institutional care, and hence in dire need of some state-managed inpatient facility.

The essay then proceeds to describe, in great detail, the progressive symptomatology of the disease as well as the modalities of professional care which may assist in the healing process.

Despite the customary advice of "get out of this climate as soon as you can" once the diagnosis of tuberculosis is entertained, he points out that placing climate *per se* as a basis of therapy is a mistaken notion. He states, "...it is a mistake to think that patients cannot get well here for they can. Many successful sanatoria are situated in much worse climates than ours, there being no climate in which patients, under otherwise suitable surroundings, cannot get well." He quotes Dr Trudeau, on the basis of his experience in the Adirondack Cottage Sanitarium, as showing a 72% cure rate for early cases of consumption.

Perkins claims that an early and accurate diagnosis becomes essential since the rate of cure is closely allied with the acuteness of the illness. "The early diagnosis being of more importance than the climate" he states.

People, he asserts, can be cured. But they must be taken from their homes to accomplish this. Certainly the general hospital will not accept them. Nor is the alms house the appropriate place for treatment. Where else might they go?

In persuasive words, he argues the merit of a local facility for the treatment of tuberculosis. "The establishment of a sanatorium would be of an economical value to the state in the return to health of members of the labor producing classes." Furthermore, in its effects upon the public health it is comparable to the purification of the water supply by removing the sources of contamination.

"As to climate I have no wish to depreciate the value of climatic conditions, such as high altitude, dry air, cloudless skies, absence of high winds and dust, an even temperature and porous soil. These are of value but no one is essential, and we are by no means wholly lacking in these things in Rhode Island."

Perkins ends with a plea to his fellow physicians to impress upon the legislature the public health and moral importance of a local establishment for this institutional care of those burdened with tuberculosis.

Herbert G. Partridge, MD writes a learned paper on the use of anesthesia in obstetrics. The author first expresses the view that obstetrical pain (a woman in travail) is brought on in some measure as a consequence of civilization and culture. In describing the recent history of anesthetic agents, he notes that Simpson, in England, first employed ether in 1847 but shortly thereafter switched to chloroform as being much superior to ether in promoting painless labor. He discards the argument that women who have not suffered would have no maternal feelings; or the parallel argument condemning the use of anesthetics as morally wrong ("in sorrow thou shalt bring forth children"). Today, he states, there is hardly an authority who does not recommend anesthesia in labor.

Partridge distinguishes between surgical and obstetrical anesthesia. In the latter its object is not to render the patient unconscious but simply to render her less acutely conscious and thus lessen the agonies of parturition.

The anesthetic should be applied during the latter part of the second stage. Some cases, he points out, likely will not need an anesthetic, particularly those who are multiparous. Anesthetics can also be used to diminish the seizures in eclampsia. He concludes: "Such is the status of anesthesia as applied to obstetrics at the present day. The ideal anesthetic is yet to be discovered. Until it is we can accomplish much with the means now at hand." *(Ed. Note: Partridge Hall, Waterman Street, on the campus of Brown University, was named in honor of Herbert Partridge.)*

Fifty Years Ago (November, 1941)

The lead article, written by Roland Hammond, MD provides a brief biography of Dr William Hunter, a noted physician and surgeon living in Newport during the mid-eighteenth century. Hunter, a close relative of the eminent John Hunter, was born in Scotland in 1729, educated in Edinburgh and migrated to Newport in 1752. His medical practice in Rhode Island was quite successful and he provided what may be the first coordinated series of lectures on anatomy and surgery given in any of the Colonies. Benjamin Waterhouse described them as follows: "They were delivered in the Court House, two seasons in succession, by cards of invitation and to great satisfaction. His collection of instruments was much larger than any professor exhibits this day. Doctor Hunter was a man of talents, well-educated at Edinburgh and a gentleman of taste in the fine arts." Hunter was also a patron of the artist Gilbert Stuart and an authority on the use of pharmaceuticals; his materia medica numbering over 273 different medications. With the onset of the Revolutionary War, Hunter, a Loyalist, threw his support to the British thus incurring the enmity of many Newporters including the Reverend Ezra Stiles, later to become President of Yale University. Hunter died unexpectedly in 1776.

JA Doherty, DMD presents a paper on the management of pathological lesions of the jaws. Diseases discussed include mandibular osteomyelitis, non-neoplastic cysts, neoplasms (epulis, osteoma, fibroma), and trauma to the jaw. He concludes: "The management of pathological lesions of the jaws entails the use of the diagnostic tripod of clinical observation, X-ray interpretation and laboratory findings. Diagnosis is based upon correlation of the facts thus derived."

Michael DiMaio, MD discusses Addison's disease in general and provides specific commentary on the management of a typical case with desoxycorticosterone acetate in oil and by pellet implantation. He presents, in detail, a case of acute Addison's disease. "The patient was maintained in excellent balance on 5 mg desoxycorticosterone acetate in sesame oil supplemented by added salt for six and one half weeks. Subsequently ten pellets of crystalline adrenocortical hormone weighing approximately 125 mg each were implanted subcutaneously in the infra-scapular region. Since discharge the patient has been on a regular diet without added salt and has been symptom free. He has maintained a normal blood pressure and has successfully resumed his activities without restriction at home and at work."

The lead editorial encourages the practicing physician to understand the principles of biostatistics.

Miscellaneous items in this month's issue include a notice by the State Department of Health that henceforth all malignant growths are to be reported to the State. A letter from the Civilian Defense Office in Washington talks of the need to coordinate civilian resources ". . . in the event of belligerent action." *(Ed. Note: This letter dated, Sept. 25, 1941 is written 74 days*

before the attack on Pearl Harbor.)

Twenty-Five Years Ago (November, 1966)

The lead article represents a paper presented by Alfred S. Ketcham, MD before the Providence Surgical Society entitled Surgical Trends in the Treatment of Cancer. The newer, more aggressive approach to cancer surgery, he contends, is ascribable to the broadening of technics now available to the educated surgeon. The newer advances in chemotherapy, cryosurgery, thermosurgery and radiosurgery are carefully reviewed and weighed. The author comments on newer preoperative evaluation procedures including the quantitation of circulating tumor cells, lymphangiography, isotope scanning and newer radiographic procedures. He also comments on technics to limit tumor cell contamination of the operative wound and the judicious use of antibiotics.

AA Savastano, MD writes a paper entitled Shoulder Straps, Girdles and Garters describing some of the orthopedic consequences of ill-fitting women's underclothing. These problems include: acromioclavicular area pressure, trochanteric bursitis, impeded venous flow in the lower extremities, and bunions, hammer toes and metatarsalgia.

OD Cinquegrana, MD writes a summary report describing the Conference on Rehabilitation sponsored by the American Medical Association, September 1966.

John E. Farrell, ScD, Executive Secretary of the Society writes on the role of the medical society in the health education of the public, citing numerous innovative examples of ways in which the medial profession has enhanced the health education of the public.

The lead editorial comments on Thanksgiving and the historic fact that the earliest Pilgrims had come to Plymouth Colony via the Dutch city of Leyden. The editorial concludes: Thus at this Thanksgiving time we who live in Rhode Island, a state founded on the principle of religious tolerance for all, a gain note with thanks that good will amongst men of different convictions is evermore apparent. As physicians we reflect on the salutary effect that such tolerance has had on the progress of medical education, and further observe its effect wherever practiced on the progress and dignity of man."

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BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk, therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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Address medical inquiries to
G.D. Searle & Co.
Medical & Scientific
Information Department
4901 Searle Parkway
Skokie, IL 60077

SEARLE G.D. Searle & Co. Box 5110, Chicago, IL 60680

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